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THE DIAGNOSTIC USE OF RADIOACTIVE IODINE IN THYROID DISORDERS

By THORKILD FRIIS and L. KORSGAARD CHRISTENSEN

Numerous, especially American, authors have described in detail the diagnostic use of radioactive iodine in disorders of the thyroid gland (2, 3, 8, 9, 10, 12, 13, 19, 21, 22, 23, 25, 27, 31, 36, 38, 42, 46, 47 and others). However as no great Danish material has hitherto been published, we consider that our series may be of interest.

The forms of measurement most commonly used are determination of the uptake by the thyroid gland of radioactive iodine and measurement of the excretion in the urine at different times after the administration of radioactive iodine. In hyperthyroidism there is a high uptake of I^{131} in the thyroid gland and a low urinary excretion; the reverse is the case in hypothyroidism (2, 3, 8, 10, 12, 13, 19, 21, 22, 23, 25, 27, 31, 36, 38, 42, 46, 47 and others). Some authors have stated that measurement of the uptake a few hours after the administration of the radioactive iodine gives better diagnostic results than determination one or two days after (3, 10, 31). The dose of I^{131} most commonly used is from 10 to 50 μc (microcurie) by mouth. The uptake is generally considered to be independent of sex, age, and ingestion of food (1, 13, 42, 46).

Several authors have stated that a determination of the radioactive iodine bound to the serum proteins (PBI^{131}) and the ratio between this and the total amount of radioactive iodine in the serum (the conversion ratio) is a valuable supplement in these measurements, especially in diagnosing hyperthyroidism (10, 18, 19, 20, 29, 38, 39, 40, 41 and others). PBI^{131} indicates the amount of the radioactive iodine administered which has been converted in a certain period into protein-bound radioactive iodine = labelled thyroid hormone, and expresses the rate of function of the thyroid gland. PBI^{131} should not be confused with the protein-bound iodine (PBI^{127}) which can be determined chemically and which is a measure of the concentration of thyroid hormone in the serum. However, the determination of PBI^{131} has not become very widely used, as it has been rather difficult to perform and has required higher doses of I^{131} (50—100 μc). The introduction of the "well-type" scintillation crystal detector was, however, a decisive change owing to the very great sensitivity of this counter, so that it is possible now to undertake this investigation with small doses of I^{131} (10—15 μc).

From Medical Department C, Copenhagen County Hospital, Gentofte (Head: *M. Siggaard Andersen*).

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MATERIAL

The series of patients comprises 226 (24 males and 202 females), all resident in the county of Copenhagen. The age-distribution is shown in Fig. 1. During the four weeks proceding the experiment none of the patients had taken drugs containing iodine (*e.g.* expectorants) or had received organic iodinated compounds for roentgen studies during the last three months, as these procedures would reduce the uptake by the thyroid gland of I^{131} (3, 8, 13, 21, 22, 36, 42, 46). All patients had a normal kidney function, estimated by serum creatinine and blood urea levels, and specific gravity of the urine. A lowered kidney function will reduce the excretion of I^{131} in the urine and thus increase the uptake in the thyroid gland (8, 22, 36, 42, 46).

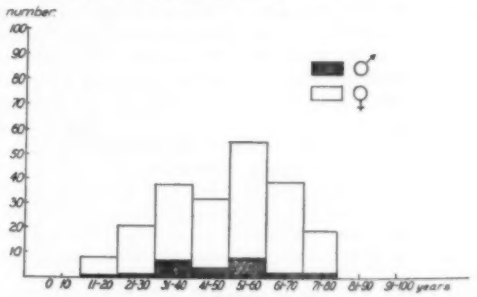

Fig. 1.
Age-distribution of series of patients. Abscissa: Age; ordinate: Number of patients.

Table I.
Classification of the series of Patients.

	Number
1. Euthyroid without thyroid disorder, with normal basal metabolic rate (90—110 per cent)	43
2. Hyperthyroid	23
3. Euthyroid with diffuse goitre	27
4. Euthyroid with nodular goitre	15
5. Hypothyroid	6
6. Euthyroid without thyroid disorder, with too low basal metabolic rate (< 90 per cent)	19
7. Euthyroid without thyroid disorder, with too high basal metabolic rate (> 110 per cent)	4
8. Euthyroid with hepatitis	14
9. Euthyroid, previously strumectomized	22
10. Patients treated with methylthiouracil	15
11. Patients treated with thyroid hormone	38
	226

Two patients who had been previously strumectomized had nodular goitre. They were included in Group 4.

Groups 6 and 7 were separated as special groups from Group 1, as it was considered that it would be of interest to examine whether these patients differed with regard to I^{131}.

The classification of the series appears from Table I. It was made on the basis of the clinical examination and observation and, in a few groups of patients, also considering the basal metabolic rate (Groups 1, 6 and 7).

TECHNIQUE

The patients were subjected to the following examinations: Determination of the basal metabolism, assessment of protein-bound iodine in the serum (PBI^{127}), measurement of the uptake by the thyroid gland of I^{131} 4, 24 and 48 hours after administration by mouth of the radioactive iodine; determination of the urinary excretion of I^{131} during the first 24 hours, and determination of PBI^{131} and conversion ratio 24 hours after administration of the radioactive iodine.

The basal metabolic rate was always determined twice in fasting patients who had been resting for three quarters of an hour.

Protein-bound iodine in serum was determined according to Barker's method (5, 15). Duplicate determinations and recovery determinations were always performed. The duplicate determinations did not differ more than 1 μg per 100 ml and the recovery determinations showed at least 80 per cent recovery of added KI*). Normal value 3.0—8.0 μg per 100 ml.

I^{131} investigations. — The isotope used was I^{131}, which is both a β and a γ emitter and which has a physical half-life of 8.1 days. The dose was from 10 to 15 μc, administered by mouth as carrier-free NaI^{131}. The dose was diluted to a volume of 100 ml. It was administered to the patients while they were fasting or, at the earliest, 2 hours after a meal. Simultaneously with this dose a similar one of exactly the same strength was prepared. The latter was used as standard and was always counted with the other countings, so that all results were given in per cent of the dose administered.

Measurements of the uptake were performed with scintillation crystal detector with NaI-thallium crystal shielded with lead and mounted on an X-ray stand so that it can be moved in all directions. The scintillation crystal detector was placed exactly 50 cm from the skin over the patient's thyroid gland. The patient was lying down. The distance was adjusted by means of two small focussing lights mounted on the lead shielding. Each of the lights projects a cross and when the crosses covered each other on the patient's neck, the distance was 50 cm. The background amounted to 100—150 counts per minute, the sensitivity of the detector was about 400 cpm for each μc of I^{131} counted at a distance of 50 cm. Immediately after the activity in the thyroid gland had been determined, that of the standard was determined at exactly the same distance; the standard, which had been diluted to 100 ml in a measuring flask, was transferred to a glass beaker with water, so that the measuring flask touched the glass wall of the beaker, which faced the detector. This arrangement was used in order that the geometrical conditions at the standard measurement might resemble as much as possible those at the measurement of the uptake by the thyroid gland in the patient, the water in the beaker corresponding to the tissue surrounding the gland. At each measurement, countings were always made twice for 1 minute, and a total count of at least 2500 was required so that the error in counting was 2 per cent at most. When this count was not obtained in 1 minute, counting was continued for 3 minutes. The uptake by the thyroid gland was expressed in per cent of the dose administered.

Excretion measurements. — The urine was collected in a special two litre bottle for a 24-hour period after the administration of I^{131} and was diluted to two litres with water. The urine bottle was then placed in a cylindrical container surrounded by six Geiger-Müller tubes.*) Background of the counter: 350 cpm; sensitivity: 1800 cpm per μc of I^{131}. Counting time: 1 minute. The standard was diluted to two litres and counted under the same conditions. The excretion was measured as per cent of the activity of the dose administered = the activity of the standard.

PBI^{131} and conversion ratio. — Venous blood was taken from the patient 24 hours after the administration of I^{131}. The activity in 3 ml of serum was determined in the well-type scintillation crystal detector (background: about 100 cpm; sensitivity: 700,000 cpm per μc of I^{131}). Counting was made for three or ten minutes, so that the total counts were at least 1000 (error in counting 3.2 per cent).

The serum proteins in three ml of serum were then precipitated with five ml of 10 per cent trichloroacetic acid and washed twice with a 2.5 per cent solution of this acid, after which the activity of the precipitate was determined in the well-type scintillation crystal detector.

*) The analyses for protein-bound iodine were performed at the Central Laboratory, Copenhagen County Hospital, Gentofte.

The counting equipment used was supplied by "Tracerlab", Boston, Mass., U. S. A.

*) The urine counter was supplied by the Karolinska Instituttet, Stockholm.

Finally, the activity of the standard, diluted 1000 times to a volume of three ml, was determined. Precipitate and serum activity were then expressed per litre of serum in per cent of the dose administered = 1000 × the activity of the standard. PBI^{131} = the activity of the precipitate.

RESULTS

Four-hour measurements of the uptake (Fig. 2 and Tables II and III).

Thirty-five out of 43 euthyroid patients (82 per cent) had an I^{131} uptake in the thyroid gland varying between 15 and 45 per cent (Group 1). These values were chosen as limits of the normal range, as a suitable distinction from the hyperthyroid group (2) was thus obtained. Two out of 23 of the latter category (nine per cent) had

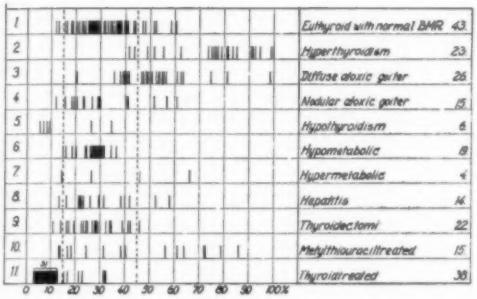

Fig. 2.

Diagram of 4-hour uptakes of I^{131} in the thyroid gland. Normal value: 15—45 per cent.

uptakes less than 45 per cent, whereas six of the euthyroid patients (14 per cent) showed uptakes above 45 per cent. Two of the euthyroid patients (five per cent) had values below 15 per cent.

Of the 23 clinically hyperthyroid patients, 12 had diffuse goitre, five nodular goitre, and six no goitre. Six patients showed pronounced exophthalmos. There was apparently no definite relation between the size of the uptake on the one hand and, on the other hand, the severity of the thyrotoxicosis, the size of the goitre, and the degree of exophthalmos. However, the two patients with a normal uptake had no goitre.

Eighteen out of 26 euthyroid patients with diffuse atoxic goitre (69 per cent; group 3) had an increased uptake. In these patients, too, no definite relation was found between the size of the goitre and that of the uptake. In contrast with this, most patients with atoxic nodular goitre (73 per cent; Group 4) had a normal uptake.

Among the patients with hypothyroidism (Group 5) four out of six had a low uptake. The one patient with a normal uptake had a slight hypothyroidism (basal metabolic rate 85 per cent, protein-bound iodine = PBI^{127}: 2.5 µg per 100 ml), the other had a pituitary myxoedema (basal metabolic rate 78 per cent, PBI^{127}: 2.9 µg per 100 ml). Most of the hyper- and hypometabolic euthyroid patients (Groups 6 and 7) had a normal uptake (21 out of 23, or 91 per cent).

The reason why patients with hepatitis were examined was that it has been stated that patients with hepatic lesions often have a high uptake of I^{131} (33) and a raised protein-bound iodine level in the serum (24). Only two out of our 14 patients showed a high uptake. Both had acute hepatitis of moderate degree with a normal protein-bound iodine serum level. Eight of this group of patients had acute hepatitis.

The strumectomized euthyroid patients (Group 9) did not differ from those of Group 1; this is in accord with the findings by other authors (12, and others).

The patients treated with methylthiouracil (Group 10) showed very varying uptakes. All were euthyroid except one, who was slightly thyrotoxic (normal uptake). There was hardly any relation between the size of any possible goitre, basal metabolic rate and level of PBI^{127}, and the size of the uptake. All patients had been treated for some months with 100 mg of methylthiouracil daily.

The patients treated with thyroid hormone (Group 11) comprised cases of myxoedema as well as patients who received thyroid hormone owing to obesity. Almost all had a low uptake (82 per cent: 31 out of 38 patients). The cause is that the administration of thyroid hormone stops the function of the thyroid gland (8, 13, 19, 42, 46). The patients were all euthyroid except two, who were hypothyroid and one who was medicamentally hyperthyroid.

It was attempted to correlate the 4-hour uptakes in Groups 1, 6 and 7 with the ages of the patients. There was apparently no relation; this is in accord with the findings by numerous authors (1, 13, 42, 46). However, Perlmutter and Riggs (35) mention that the uptake of I^{131} decreases with advancing age.

24-Hour Measurements of the Uptake

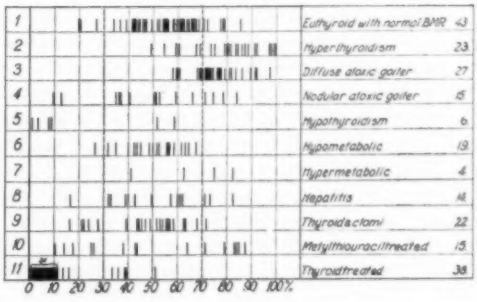

Fig. 3.

Diagram of 24-hour uptake of I^{131} in the thyroid gland. Normal value: 30—70 per cent.

The uptake after 24 hours was somewhat higher than the 4-hour uptakes (except in Groups 2 and 11). This is in accord with the fact that the uptake generally reaches maximum one or

Table II.
Mean value (m) and limits (l) for various parameters of the thyroid function in the different groups of patients (no. = number of patients).

		4-hour uptake in %	24-hour uptake in %	24-hour excretion in %	24-hour PBI ^{131} in % per l.	PBI ^{127} in μG per 100 ml
1. Euthyroid with normal BMR	No.	43	43	33	41	35
	m	31.7	54.6	37.5	0.17	5.3
	l	12.0—60.7	20.0—85.7	12 6—80.5	< 0.01—0.39	2.2—10.3
2. Hyperthyroid	No.	23	23	21	23	22
	m	69.8	80.0	14.8	1.38	9.7
	l	41.8—100.0	49.2—100.0	3.9—32.8	0.38—4.92	6.1—22.0
3. Diffuse atoxic goitre	No.	26	27	23	27	22
	m	51.7	74.3	21.3	0.10	5.1
	l	20.4—98.5	50.5—97.3	3.4—43.7	< 0.01—0.57	2.5—8.1
4. Nodular atoxic goitre	No.	15	15	12	14	13
	m	30.5	50.8	31.8	0.18	5.8
	l	11.6—56.9	9.9—84.0	11.3—72.0	< 0.01—0.47	3.8—9.7
5. Hypothyroid	No.	6	6	4	5	6
	m	15.2	21.9	66.8	0.22	2.2
	l	5.5—34.6	1.3—58.7	50.0—91.5	0.15—0.28	0.2—4.7
6. Hypometabolic	No.	19	19	19	19	19
	m	26.6	50.1	42.0	0.18	4.3
	l	15.0—36.3	26.3—67.6	27.5—64.3	< 0.01—0.58	1.5—9.7
7. Hypermetabolic	No.	4	4	4	4	4
	m	38.4	65.1	29.7	0.16	4.1
	l	14.7—66.4	40.8—82.0	12.6—51.6	0.04—0.14	2.8—4.9
8. Hepatitis	No.	14	14	11	14	13
	m	31.5	51.1	41.6	0.11	8.1
	l	13.7—58.7	16.5—82.8	24.8—54.5	0.02—0.24	4.4—17.4
9. Strumectomy	No.	22	22	19	22	19
	m	29.1	49.2	49.1	0.41	4.7
	l	10.7—55.2	16.1.—71.5	20 1—83.4	< 0.01—3.89	1.1—8.2
10. Treated with methylthiouracil	No.	15	15	12	15	13
	m	46.3	50.5	33.5	0.31	6.3
	l	13.6—86.1	10.2—87.8	6.5—55.5	0.04—1.81	2.5—6.3
11. Treated with thyroid hormone	No.	38	38	30	36	33
	m	11.1	9 7	60.9	0.16	5.1
	l	3.9—25.7	1.5—50 6	30.0—90.6	0.01—0.34	0.5—11.5

two days after the dose has been administered. The normal limits were fixed at 30 and 70 per cent, as these seemed to give the best distinction from Group 2. A samewhat greater deviation was found than in the case of the 4-hour uptake, and the overlapping between Groups 1 and 2 was somewhat greater, as six out of 43 euthyroid patients, or 14 per cent, (Group 1) had uptakes higher than 70 per cent, and six out of 23 hyperthyroid patients, or 26 per cent, (Group 2) had values below 70 per cent. It was impossible to distinguish by means of the 24-hour uptake between hyperthyroidism and patients with diffuse atoxic goitre, as 20 out of 27 of these (74 per cent) had an increased uptake.

48-Hour Measurements of the Uptake.

These measurements were performed only in 129 out of 226 cases (57 per cent). The deviation and the overlapping were even greater than in the 24-hour measurements, as three out of 33 euthyroid patients, or nine per cent, (Group 1) showed values above 75 per cent, which was fixed as the upper normal limit, while nine out of 19 hyperthyroid patients, or 47 per cent, had values below 75 per cent. The lower normal limit was fixed at 30 per cent. Eight out of 17 patients with diffuse atoxic goitre, or 47 per cent, (Group 3) had values above 75 per cent.

24-Hour Urinary Excretion of I^{131}.

These measurements were performed in 188 out of 226 cases (83 per cent). The normal limits were fixed at 20 and 65 per cent. A similar overlapping was found between Groups 1 and 2 as in the 24-hour measurements of the uptake, as four out of 33 euthyroid patients (12 per cent) had an excretion below 20 per cent, while four

Table III.
Overlapping in per cent of number of patients between euthyroid-hyperthyroid and hypothyroid patients. Euthyroid patients comprise groups 1, 3, 4, 6, 7 and 9.

	Euthyroid		Hyperthyroid	Hypothyroid
	Too high values	Too low values	Too low values	Too high values
BMR	12%	24%	5%	0%
PBI^{127}	8%	10%	27%	12%
4-hour uptake	24% (13%)	5%	9%	33%
24-hour uptake	25% (13%)	8%	26%	33%
48-hour uptake	16% (6%)	5%	47%	—
24-hour excretion	5%	14% (7%)	19% (too high values)	—
PBI^{131}	5%	—	4%	—

Figures in parentheses state the overlapping when the patients with diffuse atoxic goitre are excluded from the material.

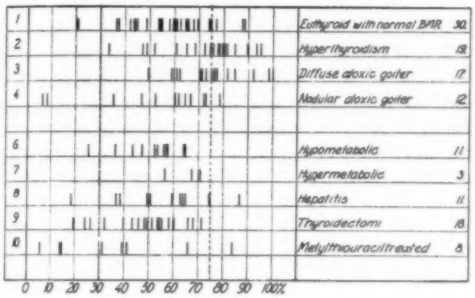

Fig. 4.

Diagram of 48-hour uptake of I^{131} in the thyroid gland. Normal value: 30—75 per cent.

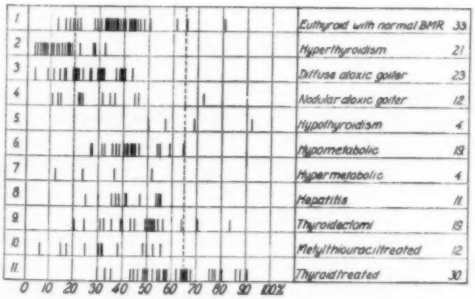

Fig. 5.

Diagram of 24-hour urinary excretion of I^{131}. Normal value: 20—65 per cent.

out of 21 hyperthyroid patients (19 per cent) had an excretion above 20 per cent. With regard to patients with diffuse atoxic goitre, the measurement of excretion of I^{131} was better than uptake determinations as only seven out of 23 (30 per cent) had too low excretion of I^{131}.

24-Hour Total Activity in the Serum.

The values varied from immeasurable values, *i.e.* < 0.01 per cent per litre of serum of the dose administered, to five per cent per litre. The high values were chiefly found in cases of hyperthyroidism and and in those who had a low uptake in the thyroid gland (Groups 2, 5 and 11); the low values were most frequently found in patients with a high uptake who were not thyrotoxic. The reason why patients with hyperthyroidism have high values is that they excrete large amounts of hormone labelled with I^{131}. These measurements had hardly in themselves any great diagnostic value.

24-Hour Protein-Bound I^{131} (PBI^{131})

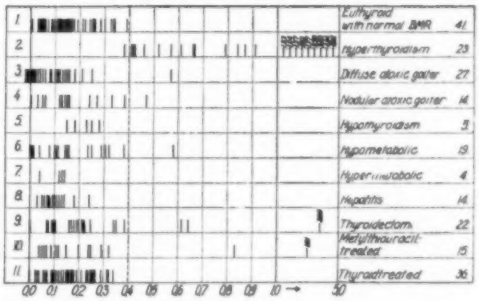

Fig. 6.

Diagram of 24-hour PBI^{131} serum level. Normal value: < 0.4 per cent per litre of serum.

In Group 1, all patients had values below 0.4 per cent per litre of serum; this was therefore fixed as the upper normal limit.

No lower normal limit could be established, as the values varied between immeasurable (< 0.01 per cent per litre) and 0.4 per cent per litre.

In the group of hyperthyroids (Group 2) all except one (95 per cent) had values above 0.4 per cent per litre. The lowest was 0.38 per cent, the highest 4.92 per cent per litre. There was apparently no relation between the severity of the thyrotoxicosis and the PBI^{131} level, nor did the size of the goitre or its nature seem to be of any significance.

Among patients with diffuse atoxic goitre (Group 3) all except one had a PBI^{131} level of < 0.4 per cent; in the one patient the uptake and the excretion of PBI^{127} and the metabolism were normal. PBI^{131} is thus much more valuable for distinguishing between euthyroid and hyperthyroid than are measurements of uptake and

excretion. On the other hand, PBI^{131} is non-contributory in the diagnosis of hypothyroidism (Group 5), as the values here varied between 0.15 and 0.28 per cent per litre.

Of the other 124 patients, seven had a raised PBI^{131} level (one patient with atoxic adenoma, one hypometabolic patient, three strumectomized, and two treated with methylthiouracil). These seven were all clinically euthyroid. The first two had a normal uptake of I^{131}, normal PBI^{127} level and basal metabolic rate. One strumectomized patient had been operated on a month ago and had a low uptake, normal PBI^{127} and metabolism. The cause of the increased PBI^{131} in this case was presumably that the remnant of the gland that had been left had been able only to maintain a sufficient output of hormone by means of a high rate of functioning. The other strumectomized patients had been operated on at least six months ago.

The second strumectomized patient had a severe exophthalmos, but normal basal metabolic rate, PBI^{127} and uptake of I^{131}. The third, who had a pronounced increase of PBI^{131}, had been treated with methylthiouracil until one week ago. The patient had a high 4-hour uptake, normal basal metabolic rate and PBI^{127}.

The two patients treated with methylthiouracil who had a raised PBI^{131} level both had a high uptake, a low protein-bound iodine level, but a normal basal metabolic rate. Both patients had a pronounced goitre and exopthalmos.

The reason why PBI^{131} was increased in the patient in whom the administration of methylthiouracil had been discontinued a few days earlier was presumably that the rate of functioning of the gland was high owing to a vigorous stimulation by thyrotropic hormone; that the three patients with severe exophthalmos had a raised PBI^{131} level is in accord with the fact that the thyroid gland in euthyroid patients with pronounced exophthalmos seems to have a high rate of functioning (16).

24-Hour Conversion Ratio.

These determinations gave less valuable results than measurements of the PBI^{131} level. All hyperthyroid patients had values above 50 per cent, which is fixed as the upper normal limit in American series (10, 18, 19, 20, 38, 39, 40, 41). However, many of the other patients (37 per cent) had values above 50 per cent.

Determinations of the Basal Metabolic Rate.

These were performed in 195 out of 226 cases (86 per cent). All hyperthyroid patients had increased values (*i. e.* > 110 per cent) except one (23 out of 24, or 98 per cent) who had a basal metabolic rate of 105 per cent, PBI^{127}: 6.4 µg per 100 ml, 4-hour uptake: 45.7 per cent, 24-hour uptake 91.5 per cent, 24-hour excretion: 17.9 per cent, and PBI^{131}: 0.52 per cent per litre of serum.

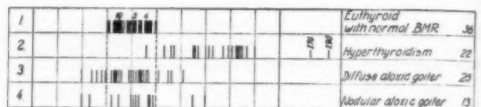

Fig. 7.
Diagram of determinations of basal metabolic rate. Normal value: 90—110 per cent.

All hypothyroid patients (8) had low values. Of the other patients, who were all clinically euthyroid (163 in all) (two treated with thyroid hormone were hypothyroid, one treated with thyroid hormone and one with methylthiouracil were hyperthyroid; these were classed with hyper- and hypothyroid), 22 had a raised (13 per cent) and 41 (25 per cent) a low basal metabolic rate.

Protein-Bound Iodine in Serum (PBI^{127}).

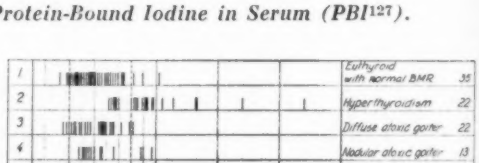

Fig. 8.
Diagram of PBI^{127} serum level. Normal value: 3.0—8.0 µg per 100 ml.

The analyses were performed in 199 out of 226 cases (88 per cent). Sixteen out of 22 hyperthyroid patients (73 per cent) had increased values. Five out of 14 patients with hepatitis (36 per cent) also had a raised serum PBI^{127} level. These five patients all had a normal uptake of I^{131}. A lowered PBI^{127} level was found in seven of eight hypothyroid patients (88 per cent), including the two patients treated with thyroid hormone who were hypothyroid. Among the clinically euthyroid patients in whom the analyses were performed (165), 11 (6.7 per cent) had increased and 20 (12 per cent) too low values.

DISCUSSION AND CONCLUSION

Our results differ in several essential respects from the American experiences.

It is striking that the normal range in the measurements of the uptake is considerably

higher than in American series (our 4-hour and 24-hour uptakes were 15—45 and 30—70 per cent respectively as compared to 10—25 and 20—50 per cent in the U. S. A.), and that our determinations of the urinary excretion are essentially lower (our excretion: 20—65 per cent as compared to 40—80 per cent in the U. S. A.) (8, 10, 12, 18, 19, 23, 36, 38, 42, 46 and others). A similar observation has been made in Finland and Sweden (25, 31). The cause hereof is unknown. If the ordinary diet contains more iodine in the U. S. A. than in Scandinavia, this can explain the difference.

It is also very striking that about 70 per cent of the patients with diffuse atoxic goitre had an increased uptake. Stanbury et al. (44) have demonstrated that patients with diffuse atoxic goitre have a high uptake of I^{131} when the goitre is endemic (*i. e.*, due to iodine deficiency), but this can hardly explain the high uptake found in our series of cases. Lamberg et al. (25, 27) have experiences from Finland similar to ours. In American series, diffuse atoxic sporadic goitre apparently has a normal, or very nearly normal, uptake (12, and others). Owing to this fact measurements of the uptake alone are not suited for estimating the function of the thyroid gland (see Table III) in the presence of a goitre. In euthyroid patients without goitre about 10 per cent have increased values (Table III). As stated by several authors, the 4-hour uptake measurements seem to be more valuable than the 24-hour uptake measurements (3, 10, 31). We have been unable to confirm the observation that toxic adenomas should have a lower uptake than toxic diffuse goitres (10, 12, 17).

The 24-hour urinary excretion is apparently a better method than measurements of the uptake if the patient has a diffuse atoxic goitre, as only 30 per cent of these patients had a too low excretion. In the absence of goitre the 4-hour uptake measurements seem to be better, as almost 20 per cent of the hyperthyroid came within the normal range at the measurements of the excretion. The latter have the advantage over the measurements of the uptake that the uncertainty owing to varying geometry from patient to patients is avoided. However, measurements of the urinary excretion are absolutely dependent upon quantitative collection of the urine.

Our patients treated with methylthiouracil differed with regard to the uptake from American experiences (3, 8, 12 and others), which show that the uptake of I^{131} is low in the course of administration of this drug. As already stated, we found varying results and have to conclude that I^{131} measurements are unsuitable in the case of patients treated with methylthiouracil.

As previously mentioned, the introduction of PBI^{131} analyses improves the I^{131} measurements to a very high degree. It has been pointed out by several authors (7, 11, 28, 30, 34) that PBI^{131} is increased in strumectomized patients, as the rest of the gland should have an increased rate of functioning. We have been able to confirm this observation only in very special cases. It is important to point out that PBI^{131} is non-contributory in diagnosing the hypothyroid cases with the dosage used in the present study.

In contrast with the findings by American authors (8, 16, 18, 19, 20, 38, 39, 40) we did not find the same good results in determinations of the conversion ratio. The cause may be that our higher uptakes contribute to reducing the denominator, so that the conversion ratio value is appreciably increased in euthyroid patients.

It is difficult to evaluate the diagnosing of hypothyroidism in the present study, as the series is too small. Two out of six hypothyroid patients had a normal uptake and excretion of I^{131}. Of the 19 hypometabolic patients, four had a low protein-bound iodine serum level. All had a normal uptake. It cannot be said whether some of these patients have actually had a slight, not clinically recognizable hypothyroidism in spite of the normal uptake.

The results of the analyses for protein-bound iodine in serum (PBI^{127}) were not as completely satisfactory in the present study as in the American series (4, 5, 6, 37, 45 and others). Only 73 per cent of our hyperthyroid patients had increased values. These results are similar to those reported in a large English series and in a Danish and a Finnish series (16, 26, 39), but somewhat lower than in the first Danish series (14).

Owing to the fact that so many cases of hyperthyroidism have normal protein-bound iodine serum levels this analysis must be considered less suitable in diagnosing hyperthyroidism than combined 4-hour uptake and 24-hour excretion measurements, even when these are not combined with PBI^{131} (Table III). Jaffe et al. (23) and Zieve et al. (48) have reported similar experiences. However, determination of the PBI^{127} level is apparently a suitable method in the diagnosis of hypothyroidism; seven out of eight cases had a low PBI^{127} level.

Contrary to several American reports (42, 48 and others), the determination of the basal metabolic rate has been rather satisfactory in our series of patients. In cases of hyper- and hypothyroidism it only very seldom fails. On the other hand, many clinically euthyroid patients have a too high or too low metabolic rate (12 and 24 per cent), to which no importance can be attached.

According to our investigations, 4-hour measurements of the uptake combined with 24-hour determinations of the PBI^{131} level are superior to other methods in the diagnosis of hyperthyroidism. All our hyperthyroid patients except three (13 per cent) showed this combination, and in two cases of these the 4-hour uptake was at the upper limit, whereas the 24-hour uptake and the PBI^{131} level were increased; in the third patient

the PBI^{131} level was at the upper limit, whereas the 4-hour uptake was decidedly increased. There was not one of the other patients, except two treated with methylthiouracil and one strumectomized patient, in whom the administration of the drug had been discontinued a short time ago, who showed this combination. Furthermore, the determination of these two parameters is both rapid and easy when the necessary aquipment is at hand.

The risk in using I^{131} for diagnostic purposes is in our opinion hardly significant when small doses are administered. As already mentioned, we used from 10 to 15 μc by mouth. The gonadal and bone-marrow irradiation dose is then about 10 milliroentgen, a very slight irradiation as compared to that which the gonads receive at abdominal diagnostic radiography (at urography, for instance, the dose is from 500 to 1000 milliroentgen). Furthermore, the patients whom it is of interest to examine will often be women over the fertile age.

The thyroid gland receives about 5—15 roentgen (18, 36), a considerably higher dose. However, with doses of up to 2.000 times higher (therapeutical doses) no case of cancer has been seen to develop in the thyroid gland in individuals with a period of observation of up to 16 years.

SUMMARY

Four-hour, 24-hour and 48-hour measurements of the uptake of radioactive iodine in the thyroid gland, 24-hour I^{131} urinary excretion measurements, determination of the 24-hour PBI^{131}, of PBI^{127} and of basal metabolic rate were performed in 226 patients with or without thyroid disorders. Four-hour measurement of the uptake combined with determination of the PBI^{131} serum level was found to be superior to the other parameters.

It is of interest to point out that the normal uptake found in the present study was much higher than that reported in American series and that our cases of diffuse atoxic goitre very often (70 per cent) had a high uptake.

References:

1) *Ackermann, P. G. & K. Iversen:* J. Gerontology 1953, *8:* 458.
2) *Arnolt, D. G., E. W. Emery, R. Fraser & A. J. G. Hobson:* Lancet 1949, *II:* 460.
3) *Astwood, E. B. & M. M. Stanley:* West. J. Surg. 1947, *55:* 625.
4) *Bardy, P. K. & B. C. Hallmann:* Am. J. Med. 1951, *11:* 619.
5) *Barker, S. B.:* J. Biol. Chem. 1948, *173:* 715.
6) *Blackburn, C. M. & M. H. Power:* J. Clin. Endocrin. 1955, *15:* 1379.
7) *Bloom, P. S. & J. Terpstra:* J. Clin. Endocrin. 1953, *13:* 989.
8) *Chapman, E. M. & F. Maloof:* Medicine 1955, *34:* 261.
9) *Christensen, B. Chr., G. Jensen & B. Strange:* Ugeskr. Læger, 1952, *114:* 1525.
10) *Mc Conahey, W. R., C. A. Owen & F. R. Keating:* J. Clin. Endocrin. 1956, *16:* 724.
11) *Fellinger, K., R. Høfer & H. Vetter:* J. Clin. Endocrin. 1957, *17:* 483.
12) *Freedberg, A. S., D. L. Chamovitz & G. S. Kurland:* Metabolism 1952, *1:* 26.
13) *Freedberg, A. S., D. L. Chamovitz & G. S. Kurland:* Metabolism 1952, *1:* 36.
14) *Friis, Th.:* Acta Med. Scandinav. 1954, *149:* 463.
15) *Friis, Th.:* Scand. J. Clinic. Lab. Invest. 1955, *7,* 336.
16) *Friis, Th. & E. Chapman:* Acta Endocrin. 1958, *27:* 207.
17) *Friis, Th., F. Fuchs, K. Iversen & T. Sv. Hansen:* Dan. Med. Bull. 1957, *4:* 6.
18) *Goodwin, J. F., A. G. Mac Gregor, H. Miller & E. J. Wayne:* Quart. J. Med. 1951, *20:* 353.
19) *Hardy, J. D. & C. Riegel:* Am. J. Med. Sc. 1951, *221:* 359.
20) *Harsha, W. N.:* J. Clin. Endocrin. 1951, *11:* 1524.
21) *Hertz, S., A. Roberts & W. T. Salter:* J. Clin. Invest. 1942, *21:* 25.
22) *Hertz, S.:* Use of radioactive iodine in the diagnosis, study and treatment of diseases of the thyroid. in S. Soskin: Progress in Clin. Endocrinology: 1950 p. 65.
23) *Jaffe, H. L. & R. E. Ottoman:* JAMA 1950, *143:* 515.
24) *Kydd, D. M. & E. B. Man:* J. Clin. Invest. 1951, *30:* 874.
25) *Lamberg, B.-A.:* Nord. Med. 1957, *57:* 818.
26) *Lamberg, B.-A., P. Wahlberg & P. J. Forsius:* Nord. Med. 1954, *51:* 571.
27) *Lamberg, B.-A., P. Wahlberg & B. Kuhlbäck:* Nord. Med. 1956, *55,* 354.
28) *Larsson, Lars-Gunnar:* Studies on radioiodine treatment of thyrotoxicosis. Stockholm 1955.
29) *Lindeboom, G. A., T. E. Hoogendijk-van Dort & J. de Jung:* Acta Med. Scandinav. 1955, *40:* 477.
30) *Lindeboom, G. A., T. E. Hoogendijk-von Dort & J. de Jung:* Acta Med. Scandinav. 1955, *40:* 487.
31) *Linderholm, H. & J. Werner:* Nord. Med. 1957, *57:* 465.
32) *de Mowbray, R. R. & A. Tickner:* Lancet 1952, *II:* 511.
33) *Mueller, R., C. C. Brauch, E. Z. Hirsch, R. S. Benua & B. M. Dobyns:* J. Clin. Endocrin. 1954, *14:* 1287.
34) *Paley, K. R., E. S. Sobel & R. S. Jalow:* J. Clin. Endocrin. 1955, *15:* 995.
35) *Perlmutter, M. & D. S. Riggs:* J. Clin. Endocrin. 1949, *9:* 430.
36) *Rall, J. E.:* Am. J. Med. 1956, *20:* 718.
37) *Salter, W. T., A. M. Basset & T. S. Sappington:* Am. J. Med. Sc. 1941, *202:* 527.
38) *Seed, L., B. Jaffe & C. Baumeister:* J. Clin. Endocrin. 1951, *11:* 1143.
39) *Sheline, G. E. & D. E. Clark:* J. Lab. Clin. Med. 1950, *36:* 450.
40) *Sheline, G. E., M. C. Moore, A. Kappas & D. E. Clark:* J. Clin. Endocrin. 1951, *11:* 91.
41) *Silver, S., M. H. Fieter & S. B. Yohalin:* Am. J. Med. 1952, *13:* 725.
42) *Skanse, B.:* Radioactive iodine in the diagnosis of thyroid disease. Uppsala 1949.
43) *Skanse, B.:* Nord. Med. 1955, *54:* 1419.

44) *Stanbury, J. B., G. L. Brownell, D. S. Riggs, H. Perimetti, E. del Castillo & J. Itoiz:* J. Clin. Endocrin. 1952, *12:* 191.
45) *Starr, P., D. W. Petit, A. L. Chaney, H. Rallman, J. B. Aiken, B. Jamieson & J. Kling:* J. Clin. Endocrin. 1950, *10:* 1237.
46) *Werner, S. C., E. H. Quimby & C. C. Schmidt:* J. Clin. Endocrin. 1949, *9:* 342.
47) *Werner, S. C., H. B. Hamilton, E. Leifer & L. D. Goodwin:* J. Clin. Endocrin. 1950, *10:* 1054.
48) *Zieve, L., B. Skanse & A. L. Schultz:* J. Lab. Clin. Med. 1955, *45:* 281.

OCCLUSION OF THE MIDDLE CERBRAL ARTERY

AN ANALYSIS OF THIRTY-SIX ARTERIOGRAPHED CASES

By HANS-HENRIK JACOBSEN and ERIK SKINHØJ

We have previously published in this periodical a clinical and arteriographic analysis of 27 cases with occlusion of the internal carotid artery (4). These cases were dominated by deprivation symptoms from the area supplied by the middle cerebral artery, and one of the purposes of the present paper is to examine whether it is possible to distinguish clinically between occlusion of the internal carotid artery and that of the middle cerebral artery, a differential diagnosis which is of special interest owing to the possibility of vascular surgery in the former and anticoagulant treatment in the latter.

MATERIAL

The series comprises 36 patients from the Neurosurgical Department and Medical Departments of Bispebjerg Hospital, the Neurological and Neurosurgical Departments of Rigshospitalet (University Hospital), Copenhagen, and the Departments of Neurology in Kommunehospitalet and Frederiksberg Hospital, Copenhagen, seen during the last 3-year period. Owing to its composition and selection, no information is given about the frequency of the disease, either absolute or relative, as compared with the total number of cases of apoplexy.

SEX AND AGE DISTRIBUTION

Twenty-four patients were males and 12 females, *i. e.*, there was a definite male preponderance, though not so pronounced as in the case of thrombosis of the internal carotid artery, where the series comprised 21 males and six females; it is, however, striking as compared with large groups of cases of apoplexy where there is a female preponderance (1). The average age was 52 years, *i. e.*, practically the same as was found in our series of carotid thrombosis. It is worthy of note that one-third of the patients were under 50 years of age, the youngest being 11 years. Thrombosis of the internal carotid and middle cerebral arteries is thus far from being only a geriatric problem.

PREDISPOSING FACTORS

Half the patients presented signs and symptoms which may be justly termed predisposing or provoking factors. Cerebral arteriosclerosis is not included here, since, as is known, it is an extremely difficult and at any rate ambiguous diagnosis to operate with on clinical criteria.

Three patients had symptoms of obliterating vascular disorders in other organs, Buerger's disease or arteriosclerosis.

Five patients had the secondary diagnosis of alcohol addiction. This was also the case in a similar, relatively large number of patients of the series with thrombosis of the internal carotid artery.

Four patients had had severe traumas of the head one, one, two and six days before the occlusion manifested itself. This finding was also stressed in the paper on carotid thrombosis, and we think it is appropriate, especially with a view to insurance, once more to emphasize the possible traumatic origin of occlusion of the carotid and middle cerebral arteries. The significance of traumas of the neck in this conjunction has been previously mentioned by Northcroft & Morgan (7) and Stierlin & v. Meyenburg (10).

Four patients had mitral disease, and the embolic origin of the occlusion was verified in the two of these who died.

Only two patients of the present series had arterial hypertension, and the thrombosis developed in both in the course of effective antihypertensive treatment. On the whole the occlusion of the middle cerebral artery is evidently a disease associated with low blood pressure, in contrast with haemorrhages in this vascular area. One third of our patients had a systolic blood pressure of 115 mm Hg or less. It is also noteworthy that all these patients developed their apoplectiform attack at rest, most frequently during sleep, as distinct from the findings in the case of haemorrhage.

CLINICAL FINDINGS AND COURSE

As would be expected, the symptomatology is characterized solely by deprivation symptoms, and the irritative phenomena caused by tumours, in the form of paraesthesiae or convulsions, were seen in only one patient. The onset was practically always definitely apoplectiform, and the

differential diagnosis from tumour, which may be impossible without arteriography in the case of thrombosis of the internal carotid artery, had only to be considered as a rare exception.

However, in the case of the post-traumatic thromboses the differential diagnosis from extracerebral haematoma was, of course, impossible without arteriography.

The hemispheric deprivation symptoms from the temporal and parietal lobes are so well-known that the clinical pictures will not be mentioned in greater detail; instead an attempt will be made to correlate the clinical features and the arteriographic findings on the basis of the two main groups into which the series can be divided arteriographically: Complete and partial occlusion of the middle cerebral artery.

As would be expected, the deprivation phenomena in the case of complete occlusion (14 patients) were massive, with hemiparalysis, both motor and sensory, severe psychic disturbance with intellectual reduction and, when the affection is present in the dominant hemisphere, pronounced aphasic disturbances which are expressive as well as central. On the other hand hemianoptic disturbances of vision are not always present, and neither the pupillary phenomena of haematomas or tumours nor pareses of the ocular muscles are seen in any single case. It is rather more remarkable that the deprivation symptoms were subtotal in two cases. This must imply that in spite of the arteriographic block the occlusion has not been complete, or that the pial anastomoses have been sufficient to maintain some degree of nervous function in the area. If so, these anastomoses, which normally are anatomically very small, must become capable of function almost instantaneously, since, as is known, irreversible degenerations occur in cortical cells after only a few minutes' anoxia. We were unable to show that the cases of this group where pial anastomoses could be demonstrated arteriographically were those which had subtotal deprivation symptoms.

In the case of partial occlusion the clinical picture is less stereotyped. We have attempted to divide this group into two according to whether arteriography showed filling of the actual sylvian vessels or only of insular branches.

In the case of the latter subdivision (12 patients) the deprivation symptoms did not differ appreciably from those seen in the group with complete occlusion. However, the motor pareses were most frequently less massive, but afferent and aphasic disturbances were almost equally severe. Three Gerstmann syndromes, however, could be differentiated here in contrast with the findings in the complete occlusions where any possible Gerstmann syndromes are lost in the massive aphasiae.

If, on the other hand, radio-opaque material appears in one or more of the sylvian vessels, the deprivation symptoms are strikingly less pronounced; this applies especially to the aphasic-gnostic disturbances and the intellectual reduction. The most conspicuous difference between the three groups appears, however, during the course of the disease. In the group of cases with complete occlusion, one died, eight remained unchanged, two showed a tendency to remission, and only one made a complete recovery (mentioned in the section on arteriographic findings as an example of arteriospasm with complete occlusion).

In the group without filling of the sylvian vessels there were two deaths, three remained unchanged, and all the other patients showed remission.

In the group in which the radiopaque substance filled one or more of the sylvian vessels one patient died (this was actually inexplicable, and autopsy afforded no satisfactory explanation either), only one remained unchanged, and the other patients showed satisfactory remission.

It may be mentioned in this connection that most of the patients had been treated with carbogen, blocking of the stellate ganglion, and anticoagulants; however, the effectiveness of these principles of treatment will not be evaluated here.

With regard to other special investigations, it may be mentioned that 17 of the patients had a lumbar puncture. The spinal fluid was normal in 14, two had a slight hyperalbuminosis, and in one case the spinal fluid contained blood. In this case, autopsy revealed considerable oedema and diapedetic haemorrhage.

ELECTRO-ENCEPHALOGRAPHY

Electro-encephalography was performed in 23 of the patients at varying times after the attack. The characteristic finding was a degenerative delta focus temporally, temporoparietally or temporofrontally, just as in the case of thrombosis of the internal carotid artery. Only in one case wat the focus irritative with spikes. The EEG was quite normal in one patient, one showed diffuse dysrhythmia, and in two cases no definite focus appeared, but there was a preponderance of abnormal potentials on the affected side.

AUTOPSIES

All the four patients who died were autopsied. In the patient with arteriographic complete block, a thrombosis was found which corresponded to the arteriographic findings. In two patients with arteriographic partial occlusion, emboli were found which were also in accordance with the arteriographic findings. In the third patient, however, no obliteration of larger branches was found, but only pronounced hyalinization of arterioles as well as oedema and diapedetic haemorrhage. This case must presumably be considered indicative of the fact that increased peripheral resistance, especially in arterioles, may lead to such a lowered blood flow in the entire vascular bed

that the condition both functionally and arteriographically becomes of the nature of a block or spasm in the large arterial branches.

ARTERIOGRAPHIC FINDINGS

The angiographic diagnosis of occlusion of the middle cerebral artery or its larger branches generally causes no difficulties, and several reports have been published on small series.

The earliest paper was published in 1936 by Løhr (6), and comprised three cases. Other series have been reported by Krayenbühl & Richter, 1952 (5), Rosegay & Welch, 1954 (9), Verjaal & Neyens, 1955 (11), Frowein, 1953 (3), and Riishede, 1957 (8).

It should, however, be realized that in certain cases there may be a less conspicuous agreement between the clinical and the radiological findings. We have thus seen two patients (who are not included in the present series) in whom the clinical picture suggested the presence of occlusion of the middle cerebral artery but whose angiograms showed unimpeded passage through all branches of the artery; here only a thorough analysis of the angiograms revealed a partly defective filling of one of the branches in the sylvian fossa with the appearance of an arteriosclerotic plaque.

In both cases there was good remission during the course of the disease, but it is possible that angiography immediately following after the attack would have shown occlusion of the arterial branch.

One of the cases included in the present series is illustrative with regard to transient occlusion of the middle cerebral artery: —

A man, aged 44, (an artiste) received a sword-thrust on the right cheek. Twelve hours later he developed impairment of consciousness and left-sided hemiparesis. After 12 hours, arteriography of the right internal carotid artery was performed; this showed complete occlusion of the right middle cerebral artery one cm from its origin. Rapid remission occurred during the week that followed, and renewed arteriography seven days after the first showed completely normal outlines and filling of the right middle cerebral artery and its branches.

A less typical case of transient complete closure of the middle cerebral artery was that of a woman, aged 21, who in a series of attacks developed left-sided hemiparesis and hemianopsia. Angiography of the right internal carotid artery showed a sudden block in the main stem of the middle cerebral artery beyond the origin of the anterior insular branches. There was good remission in the course of three weeks, and renewed angiography now showed fairly considerable, though not normal, filling of the vessels in the sylvian fossa.

Two similar cases (one with, the other without angiographic examination) have been reported by Ecker (2).

Whereas the internal carotid artery has several anastomoses with other larger systems, the middle cerebral artery can only be supplied, in the case of occlusion, retrogradely through the fine arterial anastomoses in the pia mater which arise from the anterior and posterior cerebral arteries of the same side. The presence of these anastomoses need not be substantiated; they are visible in any suitable anatomical specimen, but their possibilities of supplying sufficient quantities of blood to the area of the middle cerebral artery are very doubtful. They have been demonstrated several times at angiographies, for instance, in two cases by Rosegay & Welch, 1954 (9), and with a seriographic technique by Frowein, 1955 (3), and by Riishede (1957). The last author drew attention to the fact that an angiogram with the appearance of retrograde filling of the middle cerebral artery may be obtained in cases where the occlusion of this artery is not complete and where the filling of the peripheral branches appears somewhat later than that of the other arteries; in such cases, however, the proximal parts of the branches will contain more radiopaque material than the distal parts. We are able to confirm this, and may add that the seriographic technique will guard against this diagnostic difficulty.

In six out of our 36 cases we observed filling to a varying degree of the branches of the middle cerebral artery through the pial anastomoses from the anterior and posterior cerebral arteries. As already mentioned, we did not find, nor did we expect to find, less pronounced deprivation symptoms in these six patients than in the others. For we have had no opportunity to perform arteriography so soon after the attack that we dared attribute any physiological importance to the demonstration of these anastomoses.

On the whole it must be admitted that angiography is a rather rough method of gross anatomical examination. We have had patients other than those dealt with here in whom the clinical findings suggested the presence of thrombosis of the middle cerebral artery, but in whom neither angiographic nor pneumographic investigations showed any abnormalities, in particular no vascular obstruction being observed; but in such cases we dare not exclude the possibility that small arteries may be occluded, though this cannot be demonstrated in the radiograms.

As in the cases of thrombosis of the internal carotid artery, we have also realized that the radiological diagnosis of complete or partial occlusion of the main stem of the artery or one of its branches does not afford the pathological diagnosis. This can generally be established by coordinating the clinical and radiological pictures; but we still have a few cases like that of an 11-year-old boy in whom neither thrombosis, embolism or spasm afforded a satisfactory explanation: —

Two days before admission he hurt his head in a fall on the stairs. The next day he was confused and muddled, and had subjective diplopia.

Neurological examination showed that he was slightly torpid with left-sided hemiparesis and hypaesthesia and left-sided lower quadrantanopsia. The EEG showed a delta focus in the right temporoparietal region. Spinal fluid: normal. A thorough examination at the Cardiological Laboratory of the Copenhagen County Hospital revealed no abnormality. Arteriography showed complete occlusion of the main stem of the middle cerebral artery 1 cm from the bifurcation with filling of the anterior insular branches. There was some remission in the course of one week, and renewed angiography showed some filling of the sylvian vessels in the arterial phase, but the anterior part of the middle cerebral artery was only slightly filled and vaguely outlined.

Both in this case and in that of the 21-year-old woman reported above we had to be content with the radiological diagnosis of occlusion of the middle cerebral artery, and had no possibility of ascertaining the cause of the occlusion.

SUMMARIZING COMMENTS

The clinical picture of occlusion of the middle cerebral artery is characterized by acute deprivation symptoms arising from the temporal and parietal lobes of the affected side, very seldom with clinical or electro-encephalographic irritative phenomena, and never with symptoms from the contralateral hemisphere. A low blood pressure is predisposing, and occlusion is not infrequently due to trauma. The vessels of the area supplied by the middle cerebral artery have anastomoses only through pial vessels and, even though these may sometimes be demonstrated arteriographically, they are most frequently insufficient in cases of complete occlusion of the middle cerebral artery, and the tendency of the symptoms to remission is only very slight.

However, an arteriographic occlusion does not imply thrombo-embolic closure, but may be due to increased peripheral resistance or arteriospasm, and in some cases better filling of the vessels of the area supplied by the artery may be seen on further injection of radiopaque material at the same sitting. This indicates the value of spasmolytic treatment, such as blocking of the stellate ganglion, papaverine or carbogen during the acute phase.

If arteriography shows primary filling of one or more of the sylvian branches, the prognosis as to recovery is much better.

Occlusion of the middle cerebral artery cannot be distinguished electro-encephalographically or clinically from occlusion of the internal carotid artery, even though its clinical picture is more stereotyped and its onset more definitely apoplectiform. The differential diagnosis can only be established arteriographically, and arteriography is indicated when it is suspected that the case is one of occlusion of the carotid or the middle cerebral artery. This is not only to exclude the possibility of a tumour or a haematoma, but also with a view to any surgical treatment of the extracranial carotid thrombosis and anticoagulant treatment of the partial thrombosis of the middle cerebralt artery, one of the most important indications for this treatment, whereas complete thrombosis of the middle cerebral artery will hardly be very amenable to anticoagulant treatment.

References:

1) *Dalsgaard-Nielsen, T.:* Acta Psychiat. Neurol. Scand. 1955, *30:* 169.
2) *Ecker, A. D.:* J. Neurosurg. 1945, *2:* 479.
3) *Frowein, R.:* Acta Radiol. 1955, *46:* 381.
4) *Jacobsen, H. H. & E. Skinhøj:* Danish. Med. Bull. 1957, *4:* 240.
5) *Krayenbühl, H. & H. R. Richter:* Die cerebrale Angiographie. Stuttgart 1952.
6) *Löhr, W.:* Arch. f. Clin. Chir.: 1936, *186:* 298.
7) *Northcroft, C. B. & A. D. Morgan:* Brit. J. Surg. 1944, *32:* 105.
8) *Riishede, J.:* Cerebral Apoplexy. Aarhus 1957.
9) *Rosegay, H. & K. Welch:* J. Neurosurg. 1954, *11:* 363.
10) *Stierlin & v. Meyenburg:* Deutsche Zschr. Chir. 1920, *152:* 1.
11) *Verjaal, A. & N. Neyens:* Acta Radiol. 1955, *46:* 339.

THE ARTERIOGRAPHIC AND ELECTROENCEPHALOGRAPHIC FINDINGS IN CEREBRAL APOPLEXY

By E. FRANTZEN, B. HARVALD and H. HAUGSTED

I. ARTERIOGRAPHIC FINDINGS

During recent years, arteriography has been employed to an increasing extent in patients with apoplectic brain disease as an aid in the differential diagnosis. Employing this investigation, a series of patients may be excluded in whom the rapid development of the disease is due to tumour formation, vascular malformations, subdural haematomata, etc. Arteriography has also been of

From The Department of Neurology, Frederiksberg Hospital, Copenhagen (Head: *T. Dalsgård-Nielsen).*

significance as a method of examination in genuine cases of apoplexy as patients suffering from intracerebral haematomata can be detected when this method is employed. This fact is of therapeutic interest as certain patients with haematoma formation may be treated operatively by aspiration of the haematoma. This group of patients need not be subjected to the risk of anticoagulation therapy.

It has previously been demonstrated that the diagnosis of the various forms of apoplexy is associated with errors if clinical methods only are employed. Stürup & Fog (10), in their work on anticoagulation therapy in cerebral apoplexy from 1953 were concerned with the problems of differential diagnosis. These authors laid particular stress on the findings in the cerebrospinal fluid. Out of 43 patients treated, 12 were submitted to autopsy. In four cases, cerebral haemorrhage was present despite clear, colourless cerebro-spinal fluid. In all four cases, the albumin content was increased and the pressure was raised.

Dalsgård-Nielsen et al. have since recorded their experience with a very great number of apoplectic patients. In a paper published in 1956 based upon autopsy findings Dalsgård-Nielsen (1) found that the diagnosis of haemorrhage was correct in 65 per cent of the cases in which the diagnosis was established on clinical grounds while the diagnosis of cerebral thrombosis or embolism was verified in only 58 per cent.

Arteriographic investigations in patients with cerebral apoplexy have previously been published from Danish sources.

Olivarius & Therkelsen (8) in 1956 published a work on thrombosis of the internal carotid artery verified by arteriography. These authors had collected 16 cases from the Department of Neurology of the University Hospital, from the years 1938—1955. They found that the thrombus was localized to the left carotid artery in 12 cases and to the right carotid artery in the remaining four cases. In all of the cases the thrombus was situated extracranially; in one patient in the left common carotid artery, in 12 cases at the point of division of the artery or immediately beyond this and in three cases higher up in the course of the internal carotid artery in the neck.

The authors emphasize the significance of early diagnosis preferably before complete obliteration of the vessel has occurred, in view of prophylactic anticoagulant therapy which may possibly prevent further growth or complete occlusion of the vessel.

In 1957 Jacobsen & Skinhøj (5) published an account of 27 cases of thrombosis of the internal carotid artery, confirmed by arteriography. In the description of the arteriographic findings, they laid particular stress upon the various anastomoses which could be demonstrated. Examples of collateral flow to the occluded vessel from the internal carotid artery of the opposite side (via the anterior communicating artery), from the basilar artery (via the posterior communicating artery), and from the external carotid artery (via the ophthalmic artery) were mentioned. No correlation between the clinical symptoms and the various filled collateral systems demonstrated in the arteriogram could be revealed with certainty. The authors recommended more frequent employment of arteriography than previously in patients with cerebral apoplexy.

The most extensive Danish work concerning arteriography in cerebral apoplexy is the thesis published by Riishede (9) in 1957. The object of this work was to investigate the disturbances of cerebral circulation in patients with cerebral apoplexy by means of carotid arteriography and to undertake a diagnostic subdivision of these cases, *i. a.* on the basis of the arteriographic findings. Riishede postulates that the classical subdivision of cases of cerebral apoplexy into haemorrhage, thrombosis and embolism is quite unsatisfactory. His material consists of 100 patients over the age of 40 years. These patients were distributed in the following manner: 27 patients with arterial occlusion, 29 with insufficiency of the cerebral circulation, and 37 patients with intracerebral haematoma. None of the 29 patients with cerebral circulatory insufficiency presented, according to Riishede's criteria, an entirely normal arteriogram. In these patients, signs of arteriosclerosis or various degrees of delay in the circulation were encountered. The pathogenic factor in patients with insufficiency of the cerebral circulation must be regarded as being a disproportion between the arterial blood pressure and the resistance of the brain, which can, naturally, seldom be demonstrated in a clinical material. Riishede stressed that patients in the group of insufficiency of the cerebral circulation do not differ clinically from patients with arteriographically demonstrable occlusive processes. The diagnosis can only be demonstrated arteriographically.

MATERIAL

The material comprises 93 patients admitted to the department during the period July 1956—December 1957. The material was selected from over 100 patients submitted to arteriography, all patients being excluded in whom arteriography revealed intracranial tumours, traumatic haematomata and aneurysm.

INDICATIONS FOR ARTERIOGRAPHY

Out of the 93 patients, a total of nine patients were submitted to arteriography on account of the clinical suspicion of intracranial tumour, which diagnosis was confirmed by this investigation. The remaining 84 cases comprise solely cases of apoplexy and the symptoms will not be reviewed in detail. Patients in whom the

symptoms were very slight and transient were not submitted to arteriography. The material, thus, did not include cases of intermittent circulatory insufficiency as this is interpreted, for example, by Millikan et al. (7). These authors, in their most recent work (1958), recorded the results which they obtained in anticoagulant therapy of 317 patients among whom approximately $^2/_3$ suffered solely from deprivation symptoms lasting for up to 15 minutes with full clinical remission. Such patients were not submitted to arteriography within the period concerned.

In a certain number of cases a focus demonstrated at routine electroencephalography was the indication for arteriography although the patients concerned had shown deprivation symptoms of only brief duration lasting, however, for some days. Patients who were in poor clinical condition in the older age groups are under represented in this material. These patients either died before the investigation could be undertaken, or arteriography was not undertaken because it was considered undesirable to submit them to an investigation which would not have had any therapeutic consequences.

TECHNIQUE

Angiography was performed by percutaneous puncture of the common carotid or internal carotid artery. In only two cases, the investigation was performed bilaterally.

The reaction of the patients to the radiopaque medium was tested by preliminary intravenous injection of the preparation. During the first half of the period of investigation 35 per cent solution of Diodon was employed and in the second half 45 per cent solution of Hypaque. The majority of the patients were submitted to arteriography with local anaesthesia alone following preliminary sedation. Only a minority of the patients were investigated under general anaesthesia. Seriography was not employed but films were taken routinely in antero-posterior and lateral positions both in the arterial and venous phases. An attempt was made to carry out the investigation as early as possible after the development of the clinical symptoms but, unfortunately, practical difficulties did not render this possible to the extent desired. As regards the technique employed, the reader is referred to the article by Jacobsen & Skinhøj (15). The procedure described there was followed meticulously also in Frederiksberg Hospital.

Some trepidation has been expressed from various quarters concerning arteriographic examination of patients of this category, and complications with deterioration of the pre-existing symptoms, development of new symptoms and even death have been reported. In the present material, however, complications occurred in only one patient.

The patient was a female aged 68 years with an intracerebral haematoma. She was submitted to arteriography on both sides with an interval of two days but already prior to the second arteriography the clinical condition was very poor. The patient died 12 hours after the last arteriography. At autopsy, in addition to extensive pathological changes in the brain, haemorrhage along the vascular sheath in the mediastinum was found and, thus, concurrent causes of death were concerned.

An isolated patient complained of double vision but no demonstrable paresis of the muscles of the eye could be revealed. All the other patients tolerated the intervention very well.

RESULTS

All the arteriograms were reviewed in the light of the arteriographic diagnosis. Table I demonstrates the patient material subdivided according to the radiological findings. In the First Group consisting of a total of 30 patients, occlusion of the internal carotid artery was found in 11 cases, occlusion of the anterior cerebral in five cases and of the middle cerebral artery in 14 patients.

Table I.
Arteriographic findings in 93 patients with cerebral apoplexy.

Occlusion of Larger Vessels:	
I Internal Carotid Artery ...	11
II Anterior Cerebral Artery ..	5
III Middle Cerebral Artery ...	14
No Occlusion of Larger Vessels	
I Atrerioscleroses	30
II No Definite Abnormality ..	29
III Haematoma	4
Total	93

The arteriographic diagnosis, as mentioned previously, was established by means of a single investigation and it is obvious that the number of cases of occlusion stated here is a maximum figure. Repeated arteriographic examinations on the same side or further contralateral investigations would possibly have revealed passage through the supposedly occluded vessels. Experience in this respect was reported by Ethelberg (3) in his thesis concerning the anterior cerebral artery syndrome.

The site of the occlusion in the internal carotid artery has not been accounted for in detail. None of the patients was referred for neurosurgical treatment with the object of reestablishing the compromized circulation during the period of the investigation.

The Second Group consists of 63 patients who were distributed into two equally large sub-

groups: In one sub-group arteriosclerotic vascular changes were encountered while in the other sub-group of 29 patients, nothing definitely abnormal was found. Finally, in four cases the arteriogram showed signs of haematoma.

In arteriosclerosis the usual criteria were employed such as irregular calibration of the vessels, particularly of the internal carotid artery and the larger branches, distension or strikingly tortuous course of these vessels.

As regards Group 2, the authors consider it very probable that with more detailed evaluation of the films, changes could be found which deviated from normal conditions. Delay in the flow through the arterial tree and deficient filling of the lesser arteries, which R i i s h e d e included as abnormal findings in his thesis, have not been regarded as such in this work. The authors did not consider it possible to carry out comparisons regarding the rate of flow in the various patients, as the technical procedure employed in the X-ray photography in obtaining these arteriographs was not calculated to consider this factor.

The Third Group comprises four patients in whom the arteriogram revealed displacement of the anterior cerebral artery in all of the cases. In two of these patients the diagnosis was verified at autopsy. In one patient the diagnosis was confirmed at operation and in the last patient who survived it was established on the basis of blood-stained spinal fluid. The reason that there are only four patients with haematoma formation in this material is probably that, as mentioned previously, a series of very ill patients were excluded in whom arteriography was not performed on account of the poor general condition prior to death, or in whom this investigation was not considered desirable.

Table II.

Arteriographic findings in 93 patients with cerebral apoplexy.

	30 With occlusion of larger vessels	63 Without occlusion of larger vessels				Total %
		Arterio-sclerosis	No definite abnor-mality	Haema-toma		
		30	29	4	93	
Females	14	12	16	3	45	49
Males	16	18	13	1	48	51
Under 50	2	2	4	0	8	9
50—70	19	20	24	2	65	70
Over 70	9	8	1	2	20	21

The first section of Table II shows the sex distribution in the various groups. It appears that the distribution is similar in all of the groups. The second section demonstrates the age distribution. There is no characteristic distribution within the individual groups either. It will be observed that 9 per cent of the material are patients under the age of 50 years, scarcely ¾ were between the ages of 50 and 70 and $^1/_5$ of the patients were over the age of 70 years. The sex distribution is in accordance with that found by R i i s h e d e in his material of 100 patients but the age distribution differs. One third of R i i s h e d e's patients were under the age of 50 years compared with below $^1/_{10}$ in this present material. Half of R i i s h e d e's were between the ages of 50 and 70 years while in the present material ¾ of the patients were in this age group.

The first heading in Table III shows the side on which the arteriography was performed and this corresponds, by and large, to the side of the apoplectic insult. As in practically all other studies

Table III.

Arteriographic findings in 93 patients with cerebral apoplexy.

	30 With occlusion of larger vessels	63 Without occlusion of larger vessels				Total %
		Arterio-sclerosis	No definite abnormality	Haema-toma		
		30	29	4	93	
Right Sided Arteriography	10	16	10	2	38	41
Left Sided Arteriography	20	14	19	4	57	59
Emergency Arteriography	9	2	7	1	19	20
Arteriography Later	21	28	22	3	74	80
Previous Insult	10	9	10	0	29	31
No Previous Insult	20	21	19	4	64	69
Blood-stained C. S. F.	0	2	2	3	7	8
Clear C. S. F.	30	28	27	1	86	92
Hypertension	14	20	15	3	52	56
No Hypertension	16	10	14	1	41	44
Cardiac Disease	13	15	12	2	42	45
No Cardiac Disease	17	15	17	2	51	55

concerning patients with apoplexy, it was found that the majority of insults in this material were localized to the left hemisphere.

In only 20 per cent of the patients was the arteriography undertaken as an emergency, *i. e.* within the first week after the development of the clinical symptoms. The remainder of cases were submitted to arteriography more than a week later.

In one third of the patients, information was present concerning previous apoplectic insults while in the remainder of the patients this was the first cerebro-vascular insult.

There was macroscopic haemorrhage in the spinal fluid in only seven patients. In the remainder of the patients the cerebrospinal fluid was macroscopically clear. In all seven patients genuine admixture of blood was present. The presence of red blood cells on microscopic examination was ignored as it is difficult to estimate whether the presence of these cells in an artifact. Blood-stained spinal fluid was not found in any of the patients with occlusion while two patients with arteriosclerosis in the arteriogram and two patients in whom nothing definitely abnormal was found had blood in the spinal fluid. One patient with a haematoma had clear spinal fluid. Out of the patients who had clear spinal fluid, the protein content was raised in 16. Out of these 16, six belong to the group in which the arteriogram showed occlusion of a large vessel, eight to the group of arteriosclerosis while only one was in the group in which nothing definitely abnormal was found. One patient with hyperalbuminosis remains, *viz.*, a patient with haematoma who had otherwise clear spinal fluid.

The next heading in the table shows how many hypertensive patients were present in the various groups. The only observation of note here is the distribution of the hypertensive patients within the group showing arteriosclerosis where there are twice as many patients with abnormally high blood pressure as with normal blood pressure. The term hypertension has been taken to indicate blood pressure in which the diastolic pressure was over 100 mm Hg. on repeated measurements.

Under the last heading, the presence of heart disease in the patients in the various groups is indicated. Heart disease here is taken to include only cases with radiological or electrocardiographic signs of heart disease and among these a number of patients with perpetual arrythmia. ECG and X-ray examination of the thorax are routine methods of investigation of cases of apoplexy in this Department. Approximately half of all the patients had objective signs of heart disease. Heart disease occurred with the same incidence in all of the groups, *viz.*, in approximately half of the patients.

A brief account will be given of eight patients in whom apoplexy developed prior to the age of 50 years: In two of the patients an occlusive process was found, in two arteriosclerosis, in four nothing definitely abnormal. Six out of the eight patients had hypertension. The seventh patient had mitral heart disease and in the arteriogram occlusion of the middle cerebral artery was found. The last patient was a male aged 30 years who was a severe chronic alcoholic. All of these eight patients survived.

Table IV shows the time of admission for the patients within the various groups and the number of deaths. By and large, autopsy revealed results which might have been anticipated from the arteriographic findings. This holds particularly true for the patients in whom an occlusive process was present and for the two patients who had haematomata. In one patient the arteriogram did not reveal anything definitely abnormal but autopsy one year later revealed thrombosis of the middle cerebral artery. In five of the patients with arteriosclerosis who died, multiple foci were found at autopsy with some old and some recent infarcts. The histories of the two patients with haematomata who survived will be briefly reviewed: The first patient was a female aged 67 years who had previously been completely healthy and whose blood pressure was normal. She was admitted following the acute development of a right-sided hemiplegia. Lumbar puncture revealed blood-stained spinal fluid. Arteriography on the left side approximately one week after the insult

Table IV.
Arteriographic findings in 93 patients with cerebral apoplexy.

	30	63 Without occlusion of larger vessels				
	With occlusion of larger vessels	Arterio-sclerosis	No definite abnormality	Haema-toma		Total %
		30	29	4	93	
Hospitalized for less than 1 Month	7	6	8	2	23	25
Hospitalized for 1—6 Months	18	21	19	2	60	65
Hospitalized for more than 6 Months	5	3	2	0	10	10
Deaths	5	5	1	2	13	14
Autopsy	4	5	1	2	12	13

revealed somewhat obscure conditions and, for this reason, air-encephalography was undertaken two days later. This revealed compression and displacement of the ventricular system. In addition, a cyst-like formation connected with the ventricular system was revealed. At the same session, arteriography on the opposite side was undertaken and it could be observed that there was displacement of the anterior cerebral artery from left to right. The patient was then transferred to a neurosurgical department and at operation a cavity due to softening and filled with haematomatous masses and with wide communication with the lateral ventricle was revealed. No improvement of note occurred after operation and the patient had to be transferred in a helpless condition to a home for chronic sick.

The other patient with heamatoma who survived was a hypertensive female aged 84 who was admitted following the acute onset of right-sided hemiplegia and aphasia. Lumbar puncture revealed blood-stained spinal fluid. Arteriography approximately two weeks later showed 8 mm displacement of the anterior cerebral artery and, as haematoma was suspected, the patient was transferred to a neurosurgical department where ventriculography revealed that the haematoma was too small to benefit from operative treatment. The patient was later transferred to a psychiatric department on account of mental confusion.

DISCUSSION

By means of arteriography on a large number of patients, all of whom presented clinical signs of apoplexy, it was demonstrated that a large percentage of the patients had neither occlusion of the larger vessels nor signs of intracerebral haematoma. In this group of patients, the apoplexy had thus other causes. Even although it is considered that arteriography is possibly unable to reveal occlusion of the smaller vessels it must be presumed that a group of patients exists in whom the infarct is due to conditions other than occlusion. This presumption renders it more easily understood that pathologists frequently have to abandon the demonstration of occlusion at autopsy.

In an extensive work from 1957, Denny-Brown et al. (2) (6) demonstrated that anoxia *per se* is a sufficient cause for the development of cerebral infarction. The formation of the infarct is completely independant of the cause of the anoxia. The extent and character of the infarct are determined by the degree and duration of the anoxia on the one hand and the compensatory possibilities locally in the brain on the other, *i. e.*, the adequacy of the collateral circulation.

Analogous to this, cerebral anoxia may conceivably develop as a sequel of a thrombo-embolic vascular occlusion or failure of the circulation conditioned extracerebrally. Riishede demonstrated that the clinical picture in patients with arteriographically demonstrable vascular occlusion cannot be differentiated from the clinical picture caused by a relative cerebral circulatory insufficiency; a statement which must probably be interpreted as implying that the character and extent of the infarct are independent of the mode of development.

In two thirds of the patients, a total of 59, it must be presumed that the apoplexy was due to a relative cerebral circulatory insufficiency, as the arteriography was unable to reveal either occlusion of the larger vessels or haematoma formation. Although no numerical account can be given of the course of the disease in these patients compared with those in the group with occlusion, the authors of the present work agree with Riishede that it is impossible clinically to distinguish between these two groups.

It probably cannot be entirely excluded that among these 59 cases are some cases of intracerebral haematoma. This diagnosis may be established in isolated cases by bilateral arteriography possibly supplemented by ventriculography.

With these reservations, the authors consider that their results indicate that a group of patients exists in whom apoplexy may reasonably be explained as a sequel of a cerebral anoxia of other origin, *e. g.*, extracerebrally conditioned circulatory insufficiency of the brain which is particularly badly tolerated by patients with cerebral arteriosclerosis or other local pathological conditions of the vessels.

II. ELECTROENCEPHALOGRAPHIC FINDINGS

The electroencephalographic findings in the patients submitted to arteriography are shown in Table V. All of the patients were investigated with electroencephalography on at least one occasion. In all patients in whom the EEG was abnormal, the examination was repeated during the period of hospitalization at intervals of 14 days to one month. In evaluating the electroencephalographic findings the following were distinguished: normal EEG, focally abnormal EEG and electroencephalograms which were only diffusely abnormal. The focal abnormalities may be irritative; spikes, sharp waves or series of delta-activity or they may be non-irritative and recognized solely by irregular or possibly inhibited alpha-activity, or admixing with arrthymic slow activity. As regards localization of foci, only differentiation between foci localized anteriorly and foci localized posteriorly in the hemisphere was undertaken, and also foci which occupy the entire or practically the entire hemisphere.

Various conditions must be stressed: By far the majority of patients showed foci which might be either irritative or non-irritative, also in patients who showed normal conditions in the arteriogram or only diffuse arteriosclerosis. Foci local-

Table V.
EEG findings in 92 patients with cerebral apoplexy submitted to arteriography.

Arteriographic findings	EEG findings: Normal	Irritative focus	Non-irritative focus	Diffuse abnormality	Focus anteriorly	Focus posteriorly	Focus involving Entire hemisphere	Improvement or normalization in subsequent EEG
No definite abnormality 29 Patients	3	9	17	0	21	4	1	6
Arteriosclerosis 30 Patients	7	8	12	3	20	0	0	7
Occlusion of: — Internal Carotid Artery 11 Patients	1	5	5	0	10	0	0	0
Middle Cerebral Artery 14 Patients	0	1	13	0	14	0	0	0
Anterior Cerebral Artery 5 Patients	1	3	1	0	4	0	0	1
Haematoma 4 Patients	0	1	3	0	4	0	0	0

ized anteriorly are the most frequent and only four patients showed foci localized posteriorly and these four patients had also normal arteriograms. In all the arteriographic sub-groups both irritative and non-irritative foci occurred but irritative foci appear to be rare in patients with occlusion of the middle cerebral artery and its branches. Patients with haematomata do not deviate from the other groups either as regards the nature of the abnormality or its localization. Significant improvement or normalization were practically only observed in patients in whom the arteriogram showed signs of neither occlusion nor haematoma.

DISCUSSION

On the basis of a previous material of patients with apoplexy submitted to electroencephalography by one of the present authors (Harvald & Skinhøj 1956) it was considered that the conclusion could be drawn that severe and particularly irritative electroencephalographic foci tend to indicate haematoma formation rather than thrombosis and, conversely, that non-irritative foci suggest thrombosis. In that material, however, the diagnosis was based solely upon the clinical picture and in the majority of patients upon the findings in the cerebrospinal fluid but none of the patients were submitted to arteriography. From the present material in which the diagnosis of the apoplexy is much more certain, it appears obvious that it is impossible from the EEG to give information concerning the nature of the apoplectic insult as even patients who suffer from apoplexy on account of "insufficiency of the cerebral circulation" may present focal EEG abnormalities while, conversely, patients with arteriographically demonstrable haematomata in three out of four cases only show non-irritative foci. The observation that occlusion in the middle cerebral arterial tree most frequently causes non-irritative foci in contrast to what is the case in occlusion of the anterior cerebral arterial tree and the internal carotid artery cannot be explained satisfactorily. The reason is possibly that infarction following occlusion of the middle cerebral artery is more frequently localized to the depths of the hemisphere than is the case with infarction of the anterior cerebral artery.

The number of cases which show improvement or normalization in the electroencephalographic record is strikingly small. This may be due to the selection of the material as the majority of patients with relatively slight or rapidly transient paresis were excluded. It appears, however, uncontestable, that the possibilities for restitution are considerably greater in patients in whom the infarct is solely due to "insufficiency of the cerebral circulation" than in cases of occlusion or haematoma.

CONCLUSIONS

The conclusions which can be drawn from the above are, firstly, that the nature of the apoplectic insult cannot be determined electroencephalographically; secondly, that cases of apoplexy in which the pathogenesis is "acute insufficiency of the cerebral circulation" may cause permanent electroencephalographic changes. The observation that relatively many patients show no improvement in later electroencephalographic control examinations limits to a great extent the value of the "serial electroencephalography" so frequently employed in the differential diagnosis between tumour and vascular insult.

SUMMARY

In 93 patients suffering from cerebral apoplexy, carotid arteriography was undertaken. In 30 patients occlusion of a large vessel was found,

in four patients signs of haematoma were present while in the remaining 59 patients only arteriosclerosis or no definite abnormality was revealed. It appears, therefore, probable that the apoplectic insult in a very large group of patients is due solely to cerebral vascular insufficiency.

Electroencephalography in the same group of patients demonstrated the difficulty of differentiating between the various forms of apoplexy by means of the electroencephalogram. Signs of very massive cerebral changes may be demonstrated in patients who suffer solely from insufficiency of the cerebral circulation.

References:

1) *Dalsgård-Nielsen, T.:* Acta psychiat. et neurol. scandinav. Suppl. 1956, *108:* 101.
2) *Denny-Brown, D. & J. S. Meyer:* Neurology 1957, *7:* 567.
3) *Ethelberg, S.:* On changes in circulation through the anterior cerebral artery. Thesis. Universitetsforlaget i Aarhus 1951.
4) *Harvald, B. & E. Skinhøj:* Nord. med. 1956, *55:* 679.
5) *Jacobsen, H. H. & E. Skinhøj:* Danish M. Bull. 1957, *4:* 240.
6) *Meyer, J. S. & D. Denny-Brown:* Neurology 1957, *7:* 447.
7) *Millikan, C. H., R. G. Siekert & J. P. Whisnant:* JAMA 1958, *166:* 587.
8) *Olivarius, B. de Fine & J. Therkelsen:* Ugeskr. Læger 1956, *118:* 1193.
9) *Riishede, J.:* Cerebral apoplexy. Thesis. Universitetsforlaget i Aarhus 1957.
10) *Stürup, H. & T. Fog:* Nord. med. 1953, *50:* 1261.

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TOXIC EFFECT OF MENADIONE SODIUM BISULFITE IN PREMATURE INFANTS

By HOLGER DYGGVE

During the last three years several reports have been published on the occurrence of haemolytic anaemia, hyperbilirubinaemia and kernicterus in premature infants who had received large doses of a water soluble vitamin K preparation (the tetra sodium salt of 2-methyl-1,4 naphthohydroquinone diphosphate (Synkavit)) (1, 3, 5, 8, 9, 12, 14, 15).

Before the water soluble menadione substitutes were used instead of the natural vitamin K_1 and K_2 in the treatment and prophylaxis of hypoprothrombinaemic states in human patients and newborn infants, animal experiments had shown that these substances could produce anaemia and haemoglobinuria when administered in large doses for a long time (see 2, 14), but the preparations have been used extensively from 1940 to 1955 without any reports on undesirable side effects coming forth. In 1953 Gasser (7) described haemolytic anaemia in premature infants with Heinz inclusion bodies ("Innenkörperbildung") in a high percentage of the erythrocytes. These bodies are throught to be a sign of impending disintegration of the erythrocytes. Most of Gasser's 14 premature infants had received large doses of Synkavit, but he did not think that a distinct correlation between the use of this preparation and the laboratory and clinical findings could be established. The occurrence of Heinz bodies is not uncommon in small premature infants (Willi, 14). Allison (1,2) mentioned that he had seen a few similar cases in prematures who had received injections of 30 mg of Synkavit per day.

In the experiments with rats undertaken by Allison and coworkers Synkavit and other vitamin K substitutes were found to be much more toxic in vitamin E deficient rats than in rats receiving a normal diet. After the injection of 10 mg Synkavit per 100 g body weight haemoglobinuria and severe anaemia occurred in the course of a few hours when the rats had been on a vitamin E deficient diet for several weeks, while only slight haemolysis without haemoglobinuria was observed in rats fed on a diet containing adequate amounts of tocopheryl acetate. An aqueous preparation of vitamin K_1 caused no haemoglobinuria when injected in doses of 10 to 20 mg per 100 g body weight even in vitamin E-deficient rats.

The sodium bisulfite compound of 2-methyl-1,4-naphthoquinone was injected by the same authors into 4 vitamin E-deficient rats (10 mg per 100 g) and caused haemoglobinuria in them all. One normal rat died after the injection of the same dose of the same preparation. (This was the only experiment carried out with normal rats). Since menadione sodium bisulfite (Menadion natrium-

From the Obstetric Departments A (Head: Prof. *E. Rydberg*) and B (Head: Prof. *E. Brandstrup*) and the Paediatric Department (Head: Prof. *P. Plum*), Rigshospitalet, University of Copenhagen.
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Table 1.
Serum bilirubin in infants with birth weight 2050—2500 g.

VITAMIN K_1				MENADIONE BISULFITE			
Age (days)	Average (mg%)	Range (mg%)	Number of infants	Age (days)	Average (mg%)	Range (mg%)	Number of infants
1	3,6	1,7— 6,4	20	1	5,4	2,1— 9,2	17
2	6,5	2,1—12,4	37	2	6,9	2,1—11,9	21
3	10,0	2,4—20,7	30	3	10,7	3,9—18,8	25
4	10,9	3,6—22,0	28	4	11,7	6,1—24,0	19
5	12,1	3,0—17,8	21	5	12,6	5,4—25,3	24
6	12,0	1,5—24,0	27	6	12,2	3,9—23,5	17
7	10,6	3,0—24,3	24	7	10,3	4,3—19,0	17
8	10,7	2,2—20,0	23	8	9,9	2,0—20,0	23
9—10	8,4	2,1—19,7	27	9—10	8,4	4,4—17,8	26
11—12	5,8	2,0—11,5	16	11—12	8,0	2,8—17,1	20
13—14	4,5	1,9—11,1	14	13—14	6,9	2,0—12,8	16

bisulfit (DAK), K-vital (Leo), Hykinone (Abbott Laboratories)) is in common use especially in Denmark it was found important to examine its possible ill effects in premature infants.

MATERIAL AND METHODS

Ninety-eight premature infants with birth weight below 2500 g received 10 mg menadione sodium bisulfite intramuscularly immediately after birth. For comparison all premature infants delivered in the other lying-in department (106 in all) received 10 mg of an aqueous colloidal solution of vitamin K_1 (Phytomenadion)[1]) by intramuscular injection just after delivery. 41,8 per cent of the infants in the menadione sodium bisulfite group and 40,6 per cent of those in the vitamin K_1 group weighed less than 2000 g. The remaining infants weighed between 2000 and 2500 g at birth. All cases with blood group incompatibility were excluded. Blood group determinations were carried out in all mothers and infants. Coombs' test and a direct conglutination test (Munk-Andersen, 11) was performed on umbilical cord blood from all included cases. A search for irregular immune antibodies in the mother's serum was made in Rh-negative mothers and otherwise when indicated.

The few cases in which the mothers had received vitamin K preparations before delivery and when the infants received more than one injection of vitamin K were also excluded. No blood transfusion or exchange transfusions were given to the infants. Besides vitamin K no other medication was used except sodium penicillin, oxygen and glucose or saline in a minority of the cases.

Determinations of total serum bilirubin (method of With, 16), reticulocyte counts and haemoglobin (Sicca Haemometer, Testa laboratorium) were performed every other day. Icterus index was also measured on a "Sicca icterus apparatus" (Testa laboratorium). While good correlation was found when the bilirubin values were plotted against simultaneous values for the icterus index when serum bilirubin was below 10 mg per cent (corresponding to an icterus index of about 90) the values were so dispersed above 10 mg per cent that the method had to be abandoned.

RESULTS

Bilirubin.

Average and range of total serum bilirubin values on the different days of life in infants with birth weight between 2000 and 2500 g are presented in Table 1 and Fig. 1.

Practically no difference between the values on the first 10 days of life was found, but from the eleventh to the fourteenth day the level is bisulfite than in those who received vitamin K_1. higher in the infants receiving Menadione sodium

[1]) The preparation, which is named Konakion abroad, was kindly furnished from Hoffmann-La Roche & Co. A. G., Basel.

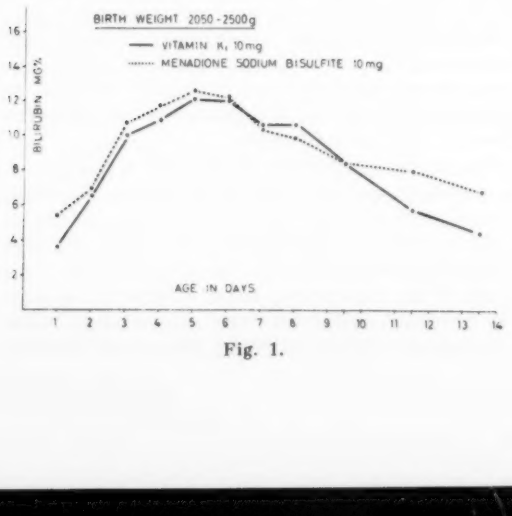

Fig. 1.

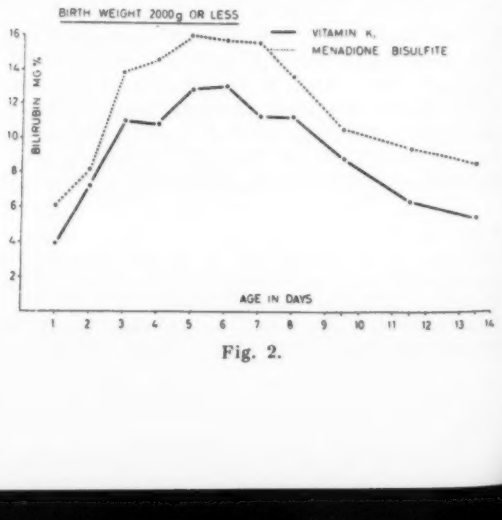

Fig. 2.

Table 2.
Serum bilirubin in infants with birth weight 2000 g or less.

VITAMIN K_1				MENADIONE BISULFITE			
Age (days)	Average (mg%)	Range (mg%)	Number of infants	Age (days)	Average (mg%)	Range (mg%)	Number of infants
1	3,9	1,4— 6,4	9	1	6,1	3,6—10,9	11
2	7,2	2,1—20,0	29	2	8,2	2,9—18,0	17
3	11,0	5,2—24,7	22	3	13,9	6,0—27,2	18
4	10,8	1,4—23,9	26	4	14,6	7,3—26,7	14
5	12,8	4,9—20,3	20	5	16,0	9,0—25,3	20
6	13,0	2,1—21,8	20	6	15,7	8,6—24,8	16
7	11,2	2,6—19,5	15	7	15,6	4,8—21,9	13
8	11,2	2,1—21,2	17	8	13,6	5,3—21,4	17
9—10	8,7	1,7—22,0	27	9—10	10,5	3,3—20,1	16
11—12	6,3	1,9—13,3	10	11—12	9,4	4,0—15,4	12
13—14	5,4	1,9—10,5	6	13—14	8,5	3,2—11,8	16

Table 2 and Fig. 2 show total serum bilirubin values in infants weighing 2000 g or less at birth.

Among the smallest prematures a definite and constant difference was found, the bilirubin levels being highest throughout the two first weeks of life among the infants who received the Menadione bisulfite compound. 15 of 98 prematures (15,3 per cent) receiving this preparation had a total serum bilirubin of 20 mg per cent or more, whereas 11 of 106 (10,4 per cent) receiving the vitamin K_1 preparation had 20 mg per cent or more at at least one of the determinations.

Haemoglobin.

Haemoglobin percentages in infants weighing 2000—2500 g at birth can be seen in Table 3 and Fig. 3.

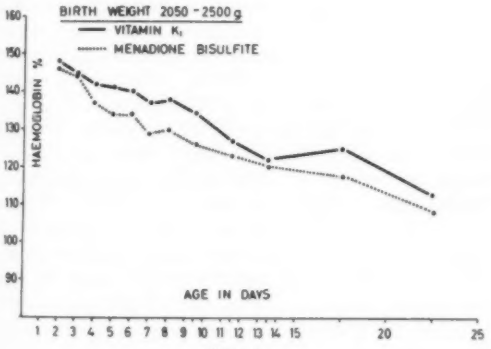

Fig. 3.

The haemoglobin values were a little lower when the infants had received the bisulfite compound at birth. Although the difference was only very small it is astonishing that the average haemoglobin level was always highest in the vitamin K_1 group. No case of severe anaemia was encountered either in this weight group or among the smallest prematures (Table 4) who received Menadione sodium bisulfite.

As evidenced in Table 4 and Fig. 4 the drop in haemoglobin through the first three weeks of life was most pronounced among the smallest prematures when they had received the bisulfite preparation after delivery.

Table 3.
Haemoglobin percentage in infants with birth weight 2050—2500 g.

VITAMIN K_1				MENADIONE BISULFITE			
Age (days)	Average Hb%	Range min. max.	Number of infants	Age (days)	Average Hb%	Range min. max.	Number of infants
1	152	129—180	30	1	153	128—175	23
2	148	112—172	30	2	146	120—150	17
3	145	119—173	30	3	144	114—165	23
4	142	101—162	29	4	137	110—156	23
5	141	120—168	28	5	134	114—150	26
6	140	100—165	24	6	134	120—144	19
7	137	101—158	26	7	128	95—150	20
8	138	92—150	22	8	130	109—145	20
9—10	134	108—150	37	9—10	126	108—140	25
11—12	127	105—145	18	11—12	123	94—140	22
13—14	122	102—140	11	13—14	120	105—138	12
15—20	125	118—142	5	15—20	118	99—135	14
21—25	113	110—120	3	21—25	108	90—131	9

Table 4.

Haemoglobin percentage in infants with birth weight 2000 g or less.

VITAMIN K_1				MENADIONE BISULFITE			
Age (days)	Average Hb%	Range min. max.	Number of infants	Age (days)	Average Hb%	Range min. max.	Number of infants
1	155	129—180	16	1	155	114—180	15
2	150	113—177	20	2	144	102—165	17
3	146	113—176	23	3	142	114—162	20
4	146	112—172	23	4	139	119—165	17
5	144	114—165	20	5	136	113—150	21
6	140	98—155	18	6	132	108—162	17
7	139	113—156	17	7	134	110—143	14
8	137	114—160	17	8	130	104—147	19
9—10	136	110—150	29	9—10	129	108—141	20
11—12	135	120—150	14	11—12	125	102—144	20
13—14	138	120—145	10	13—14	120	98—138	14
15—20	122	110—131	11	15—20	111	93—130	10
21—25	110	90—120	7	21—25	97	83—108	8

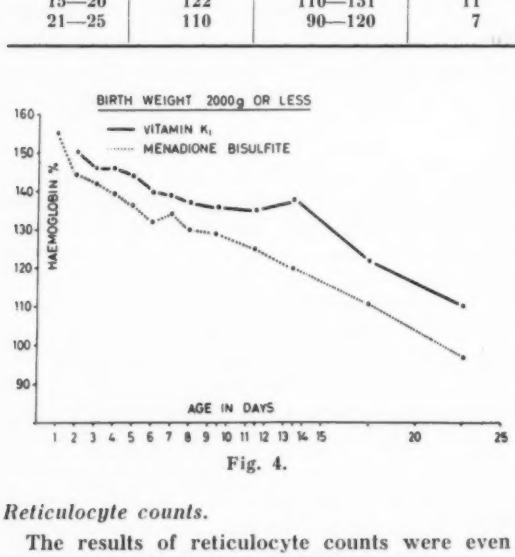

Fig. 4.

Reticulocyte counts.

The results of reticulocyte counts were even more scattered than the bilirubin and haemoglobin values without any constant correlation between these three values being found. Generally the highest reticulocyte count was found just after birth, but sometimes a rise was seen during the first or second week of life.

The average number of reticulocytes was, when the highest count found in each individual infant was included, 3,2 per cent among 57 cases weighing between 2000 and 2500 g who received Menadione bisulfite, and 3,0 per cent in 63 infants of the same weight group who got Konakion. Thus no difference was found among the biggest prematures. On the other hand a distinct difference was found among the infants with birth weight below 2000 g, the average number of reticulocytes among 41 cases receiving the menadione bisulfite preparation being 6,3 per cent, whereas only 3,6 per cent was found in 43 infants who were given vitamin K_1.

DISCUSSION

No previous investigations concerning toxic influence of menadione sodium bisulfite in premature infants seem to have been reported. In this investigation slight toxic effects of this vitamin K preparation was observed when it was given as a single intramuscular injection in a dose of 10 mg immediately after birth and compared with the effect of an aqueous suspension of vitamin K_1. Among prematures with birth weight ranging from 2000 to 2500 g no significant hyperbilirubinaemia, anaemia or reticulocytosis was found but such alterations were seen among the small prematures weighing 2000 g or less at birth. Among 41 infants in this weight group receiving Menadione sodium bisulfite at birth 10 (24.4 per cent) had a maximum serum bilirubin level of 20 mg per cent or more, whereas only 6 out of 43 (14 per cent) small prematures receiving vitamin K_1 reached the same high level. Among the bigger prematures (birth weight 2050—2500 g) the difference in the number of cases with serum bilirubin values above 20 mg per cent was negligible (8.8 per cent in the Menadione bisulfite group and 7.9 per cent in the vitamin K_1 group, comprising 57 and 63 cases, respectively).

Bound & Telfer (3) found that 38 per cent of 55 premature infants who received 30 mg of Menadiol sodium diphosphate (Synkavit), 10 mg intramuscularly on each of the first three days of life, reached above 18 mg per cent of serum bilirubin on the fifth day, while only 4 per cent of 51 prematures who received but one mg of the same substance had more than 18 mg per cent at the same time after delivery. The average bilirubin value was 9.7 mg per cent on the fifth day among the prematures receiving 1 mg of Synkavit and 15.4 mg per cent among those who were given 30 mg. Meyer & Angus (9) and Nitsch (12) also found higher serum bilirubin levels when 30 or 10 mg of menadiol sodium diphosphate was given to premature infants than when no vitamin K or only one mg of vitamin K_1 was administered. The average bilirubin values found by these authors were

lower than those reported by Bound & Telfer and in this paper.

In another study (6) definitely higher serum bilirubin levels were found in premature infants to whom a prophylactic intramuscular dose of 10 mg of Menadiol sodium diphosphate was given than in those who received vitamin K_1. Willi (14, 15) and Zbinden et al. (17) found in animal experiments that Menadiol sodium diphosphate regularly produced Heinz inclusion bodies, while vitamin K_1 in doses as high as 100 mg per kg intravenously caused no alterations of the erythrocytes of mice or dogs. The formation of Heinz bodies after injection of Synkavit into mice could not be prevented with vitamin E (Willi, 15). The significance of the low levels of vitamin E found in the blood of newborn infants has not yet been disclosed.

Since large doses of various vitamin K substitutes cause severe anaemia and haemoglobinuria in animals it is probable that the hyperbilirubinaemia caused in premature infants by these drugs depends on haemolysis of the erythrocytes. Although Zbinden et al. could prove no increased osmotic fragility in their animal experiments the small decrease in haemoglobin and the increased number of reticulocytes found in our premature infants to whom the menadione bisulfite compound was administered seem to support this view.

SUMMARY

Two groups of about 100 premature infants (40 per cent of each group weighing less than 2000 g) received either the sodium compound of 2-methyl-1,4 naphthoquinone or vitamin K_1 as an aqueous colloidal solution. Both preparations were given as a single intramuscular injection containing 10 mg of the substance immediately after birth. All cases with blood group incompatibility were excluded.

Determinations of total serum bilirubin, haemoglobin and reticulocyte counts were done every other day. While only minor differences were found in infants weighing more than 2000 g at birth, the smallest prematures had definitely higher serum bilirubin levels and reticulocyte counts, and lower haemoglobin values, when menadione sodium bisulfite was given, than when vitamin K_1 had been administered.

Among the infants with birth weight below 2000 g serum bilirubin levels above 20 mg per cent were found in 24 per cent of those receiving the bisulfite preparation and in 14 per cent of the vitamin K_1 group.

Since minor toxic effects were demonstrated after the injection of 10 mg of Menadione sodium bisulfite in premature infants, the dose of this drug should not exceed a single parenteral dose of 2 or 3 mg. Especially if repeated injections of vitamin K are required in newborn infants, vitamin K_1 as an aqueous solution should be preferred.

References:

1) *Allison, A. C.:* Lancet 1955, *1:* 669.
2) *Allison, A. C., T. Moore & I. M. Sharman:* Brit. J. Haemat. 1956, *2:* 197.
3) *Bound, J. P. & T. P. Telfer:* Lancet 1956, *1:* 720.
4) Council on Drugs of the American Med. Ass.: JAMA 1957, *164:* 1331.
5) *Crosse, V. M., T. C. Meyer & J. W. Gerrard:* Arch. Dis. Child. 1955, *30:* 501.
6) *Dyggve, H.:* To be published.
7) *Gasser, C.:* Helvet. paediat. Acta 1953, *8:* 491.
8) *Laurance, B.:* Lancet 1955, *1:* 819.
9) *Meyer, T. C. & J. Angus:* Arch. Dis. Childh. 1956, *31:* 212.
10) *Moore, T. & J. M. Sharman:* Lancet 1955, *1:* 819.
11) *Munk-Andersen, G.:* Acta pathol. et microbiol. Scand. 1956, *38:* 259.
12) *Nitsch, K.:* Klin. Wschr. 1957, *35:* 363.
13) Nutrition Reviews: 1957, *15:* 331.
14) *Willi, H.:* Helvet. paediat. Acta 1956, *11:* 325.
15) *Willi, H.:* Annales paediat. Fenniae 1957, *3:* 283.
16) *With, T. K.:* Acta med. Scand. 1943, *114:* 426.
17) *Zbinden, G., K. Schärer & A. Studer:* Schweiz. med. Wschr. 1957, *97:* 1238.

SARCOMA OF THE STOMACH

By P. AAGAARD

Compared with carcinoma of the stomach, sarcoma of the stomach is a rare disease. However, the clinical findings and pathological anatomy of a not inconsiderable number of cases have been described (*i. a.* by Palmer 1950, Sønder 1950, Fries 1951, Crile, Hazard & Allen 1952, Engberg 1953, Jordan, Heard & Waldron, Eker, Efskind & Zimmer 1956). Although the clinical picture of the disease is thus recognized, the significance of publishing histories of this rare condition must be emphasized (Grasser 1953) as it appears to have a considerably more favourable prognosis than carcinoma of the stomach. This holds particularly true for leiomyosarcoma which is extremely rare. Only a few cases have hitherto been published. The significance of establishing the differential diagnosis between sarcoma and carcinoma of the stomach lies in the fact that the prognosis for

From Surgical Department D (Head: Professor *E. Husfeldt*), and Surgical Department R (Head: Professor *Fr. Therkelsen*). Rigshospitalet, University of Copenhagen.

sarcoma (particularly leiomyosarcoma) is considerably more favourable than for carcinoma. In addition, lymphoid sarcomata are sensitive to radiation and should, therefore, be treated with X-ray radiation either as follow-up therapy after operation or as the only form of palliative treatment in the inoperable cases.

As examples of the more favourable prognosis which exists particularly as regards leiomyosarcomata it may be mentioned that Marshall & Meissner (1950) following operative treatment in 37 cases of sarcoma of the stomach found that 44 per cent had survived a five-year period. Crile, Hazard & Allen (1952) found after operation upon 19 cases that 68 per cent were free from symptoms after five years.

MATERIAL

During the period 1945—1957, 370 cases of cancer of the stomach were treated in the Surgical Departments D and R, Rigshospitalet. No histological investigation was undertaken in 61 cases which were inoperable. Out of the 309 cases in which histological examination was undertaken, four cases of sarcoma were encountered, *i. e.* 1.3 per cent (Marshall & Meissner 1950 found 3.7 per cent, Fries 1951 0.8 per cent and Eker & Efskind 1956 2.5 per cent). In the present material, the sarcomata comprize one leiomyosarcoma (developed from smooth musculature) and three lymphoid tumours (developed from lymphatic tissue).

CASE HISTORIES

Leiomyosarcoma.

The patient, a female aged 37 years, was admitted for the first time in 1954. Three months prior to admission she developed violent hœmatemesis and melaena without preliminary symptoms. She was treated with blood transfusions and low-residue diet. X-ray examination showed a mark which was interpreted as an ulcer niche, slightly below the middle of the lesser curvature. On admission to Rigshospitalet, the general condition was good. No tumour could be felt in the epigastrium. Neither occult bleeding nor anaemia were present. No loss of weight had occurred. X-ray examination of the stomach did not reveal any definite abnormality. With the provisional diagnosis of gastric ulcer, laparotomy was undertaken and a tumour approximately 8 × 10 cm originating from a point corresponding to the angle of the stomach was found. The tumour could easily be isolated and was removed together with a piece of gastric mucosa approximately 5 × 5 cm. As microscopic examination of a frozen section revealed it to be a leiomyosarcoma, resection was not undertaken and operation was restricted to the above-mentioned excision through healthy tissue. No post-operative complications occurred. The patient felt well for the first two months after operation but thereafter, pain and diarrhoea developed and melaena occurred on an isolated occasion. As recurrence could not be excluded, laparotomy was repeated approximately two years after the first operation but no signs of recurrence nor metastases were found.

Lymphoid Tumours.

1. Male aged 69 years. For approximately two years, the patient had experienced enlarged glands in the abdomen, inguinal regions and axillae. For approximately six months, he had experienced pain in the epigastrium, vomiting, fatigue and loss of weight. On admission, the patient was thin, the ESR was raised and anaemia (Hb 85 per cent) and achlorhydria were present. X-ray examination of the stomach showed a filling defect as large as a walnut at the fundus of the stomach. At operation, a large tumour was found in the fundus and enlarged glands were observed around the spleen and the left gastric artery. Total gastrectomy with removal of the spleen and the tail of the pancreas was undertaken. Microscopic examination of the tumour revealed it to be a lymphosarcoma. The patient died five days after operation, from peritonitis.

2. Male aged 77 years. The patient had suffered from constipation for approximately six months and from isolated episodes of melaena. In addition, he had experienced pain in the upper part of the epigastrium. No vomiting had occurred. On admission, the patient was thin, the ESR was raised but no anaemia. X-ray examination of the stomach showed nodular defects in the region of the fornix. At operation, a tumour as large as a clenched fist was encountered in the fundus of the stomach. The tumour extended as far up as the cardia and 5—6 cm down along the curvatures. Hard glands were found around the large arteries. Resection of the proximal part of the stomach was undertaken. Microscopic examination revealed a lymphosarcoma. The patient died 21 days after operation from peritonitis.

3. Male aged 80 years. The patient had experienced moderate pain, a sensation of pressure in the epigastrium for approximately six months. No vomiting, melaena nor haematemesis had occurred. On admission the patient was in relatively good general condition. Neither anaemia nor occult haemorrhage was present. Achlorhydria was present. X-ray examination of the stomach showed large irregular filling defect distally on the greater curvature. At operation, a large ulcerated tumour in the region of the pylorus was found. Hard glands were present in the neighbourhood but no metastases to the liver were observed. Resection of the stomach by the Billroth I method was performed. Microscopic examination revealed a lymphosarcoma. The patient died eight months after operation with signs of recurrence. No autopsy was performed.

The first history is typical of leiomyosarcoma. The general condition was good, there were no striking subjective symptoms and the condition made its appearance by haemorrhage. Local excision of the tumour only was performed and not resection, and despite this, the patient survived in good health for two years after operation. This is in accordance with the general conception that the prognosis is much more favourable in cases of leiomyosarcoma than in cases of carcinoma.

The three other cases show the characteristic features of lymphoid tumours which, as regards the clinical picture and prognosis, resemble anaplastic carcinomata. The general condition is poor and striking subjective symptoms with anaemia and loss of weight were present. In all three cases,

elderly patients were concerned. Two of the patients died shortly after operation from peritonitis and the third died eight months later probably on account of recurrence.

It appears from the case histories, that the correct diagnosis was not established in any of the cases prior to operation. The lymphoid tumours were interpreted at X-ray examination as carcinomata while the leiomyosarcoma was thought to be an ulcer.

The diagnosis of sarcoma of the stomach is difficult. Nothing exists to differentiate it clinically from carcinoma. X-ray examination and laboratory investigations are not of great assistance but the diagnosis is frequently not established until the specimen removed at operation is subjected to microscopic examination. It should be strongly emphasized that microscopic investigation should always be undertaken even in inoperable cases on account of the more favourable prognosis in leiomyosarcoma and the radio-sensitivity of lymphoid tumours.

SUMMARY

Four cases of sarcoma of the stomach are presented (one leiomyosarcoma and three lymphoid tumours). The characteristic features and the more favourable prognosis of leiomyosarcomata are discussed. The significance of routine microscopical investigations of the specimens from operated is stressed.

References:

Crile, G. Jr., J. B. Hazard & K. L. Allen Ann. Surg. 1952, *135:* 39.

Eker, R., J. Efskind & J. Zimmer: Acta chir. scand. 1956, *3:* 386.

Engberg, J.: Nord. Med. 1953, *50:* 1610.

Fries, B.: Nord. Med. 1951, *45:* 277.

Grasser, C. H.: Radiol. clin. 1953, *22:* 265.

Jordan, G. L. jr., B. G. Bolton, J. G. Heard & G. W. Waldron: Surg. Gynec. and Obst. 1955, *100:* 453.

Marshall & Meissner: Ann. Surg. 1950, *131:* 825.

Palmer, E. D.: Ann. J. Digest. Dis. 1950, *17:* 186.

Sønder, P.: Ugeskr. Læger 1956, *112:* 702.

THE BASOPHILIC SUBSTANCE OF THE GASTRIC CHIEF CELLS AND ITS RELATION TO THE SECRETORY PROCESS

SUMMARY OF THESIS

By JAN WEBER

Cellular protein synthesis is accompanied by active metabolism of nucleic acid. By methods based upon the special absorption of nucleic acid in ultra-violet light a high nucleic acid content has been demonstrated in cells during growth and division and in certain gland cells (Caspersson). The nucleic-acid-containing combinations may be coloured specifically by Einarson's staining method with gallocyanin chromalum. This method of staining has proved of great significance in investigating the functions of the nervecells during normal and pathological conditions (Einarson, Lorentzen, Krogh, Bech).

A series of gland cells produce protein containing secretions. The cytoplasm of these cells contains great quantities of nucleic acid during the formation of secretion. Employing Einarson's staining method in connection with a photometric apparatus the content of nucleic acid in the gland cells can be studied during secretion as the intensity of the staining depends solely upon the content of nucleic acid (Oram).

The nucleic acid metabolism in the cells appears, thus, to be intimately connected with synthesis of protein and, therefore, of great significance for the fundamental functions of the cells. Gland cells are suitable for a study of these processes as they may be brought into various conditions of function by relatively simple procedures.

To elucidate the more intimate relationship between the function of the cells and the content of nucleic acid, investigation of the chief cells of the stomach which form a proteincontaining secretion, was elected. The process of secretion was produced partly by stimulation with pilocarpine and partly by feeding. Rats and cats were employed in the experiments.

To estimate the content of nucleic acid a photometric apparatus designed by Hansen & Einarson was employed. This photometer permits measurement of transmission of light directly on the stained preparation. Further, measurements in a very limited area within the individual cells are possible. Following stimulation, it was found that the chief cells had discharged their secretion. Simultaneously, as a link in the reformation of secretion, accumulation of nucleic acid-containing compounds was found, first in the basal part of the cells and later in the entire cytoplasm.

When the cells were observed at varying intervals after stimulation it was found that rhythmic variations occurred in the nucleic acid content of the cytoplasm. These rhythmic variations were

encountered both after stimulation with pilocarpine and after feeding, but the processes appeared to be more rapid following stimulation with pilocarpine. The content of nucleic acid was found to be inversely proportional to the quantity of secretion in the glands at a given time in the process of secretion. Thus, no doubt exists that the presence of nucleic acid in the cytoplasm is an essential condition for the formation of secretion.

Simultaneously with changes in the nucleic acid content of the cytoplasm, morphological changes in the nuclei were observed suggesting their co-operation in the secretory process. Thus, in the active, *i. e.*, secretion-forming, cell a large nucleolus was found and accumulation of nucleic acid at the nuclear membrane. In the resting cell, an indistinct nucleolus was found and the chromatin was evenly distributed throughout the entire caryoplasm. In the latter case, no concentration of nucleic acid at the nuclear membrane was found. This morphological expression of the resting phase was, however, found only in cats. In rats, signs of secretion formation were always present even after prolonged periods of fasting.

In agreement with previous investigations (L a g e r s t e d t) it must be presumed that the formation of secretion in the chief cells of the stomach follows the same processes as in other cells during the formation of protein. The nucleus forms ribosenucleic acid (RNA) which accumulates around the nucleolus. The RNA-containing compounds wander thence through the nuclear membrane out into the cytoplasm where they take part in the formation of more complex protein substances, *e. g.* secretion.

In investigation of the nucleic acid metabolism in cells during function, it is of significance to extend the investigation to as many stages of the function as possible. An impression can thus be gained of the entire process. In this manner, also, a possibility exists of revealing deviations from the normal.

Staining with gallocyanin chromalum renders possible a relatively easy and simultaneously markedly objective method of estimating the nucleic acid content in the cells. This method may, therefore, be employed with advantage both for investigation of the function of a series of gland cells during normal and pathological conditions and in the study of the processes associated with cellular protein synthesis in general.

Reference:

Weber, Jan: Acta Anatomica 1958, *33:* suppl. 31.

MEDICO-STATISTICAL INFORMATION FROM DENMARK FOR THE YEARS 1956 AND 1957

By KAREN DREYER and ERNA FRANDSEN.

The information in Table 1, together with that of Table 2, showing the number of reported cases of epidemic diseases, indicates that the epidemic morbidity was remarkably high in 1957. The heavy increase from 1956 to 1957 was mainly due to influenza of which 544,613 cases were notified against 115,203 in 1956. The peak was reached during the months of October and November with 159,956 and 168,306 notified cases respectively, but also the months of March and April showed rather high incidence, viz 39,767 and 44,630 cases respectively. The age distribution of influenza cases in 1957 was as follows: Under 1 year 1 per cent, 1—4 years 10 per cent, 5—14 years 25 per cent, males 15—64 years 30 per cent, females 15—64 years 29 per cent, males 65 years and over 2 per cent, and females 64 years and over 3 per cent.

Only 26 cases of acute anterior poliomyelitis were notified in 1957, namely 10 paralytic and 16 aparalytic, as against 191, 37 and 154 respectively

Table 1.

Population:	
Census October 1st, 1955: 4,448,401.	
Estimated, July 1st, 1957: 4,487,800.	
Live-born:	1957 75,264 = 16.8 per 1,000 population
	1956 76,725 = 17.2 per 1,000 population
Still-born:	1957 1,169 = 1.5 per cent of total births
	1956 1,357 = 1.7 per cent of total births
Deaths: total	1957 41,730 = 9.3 per 1,000 population
	1956 39,590 = 8.9 per 1,000 population
Deaths: under 1 year	1957 1,758 = 23.4 per 1,000 live-born
	1956 1,914 = 24.9 per 1,000 live-born
Notifiable diseases:*)	
	1957 1,125,385 = 251 per 1,000 population
	1956 716,771 = 160 per 1,000 population
December 31st, 1956.	
Practising physicians:	5,172 = 1 per 864 inhabitants.
Practising dentists (total):	2,200 = 1 per 2,030 inhabitants.
Dentists with own practice:	1,421 = 1 per 3,143 inhabitants.
Pharmacies: 351 = 1 per 12,725 inhabitants.	
Practising midwives: 679 = 1 per 1,567 women	in the age group 15—49 years.

*) Except venereal diseases, delirium tremens and scabies.

From the National Health Service, Statistical Section. Head: *Marie Lindhardt.*

Table 2.

The epidemic morbidity in Denmark 1957 and 1956.

	Reported cases		per 100,000 pop.	
	1957	1956	1957	1956
Typhoid fever	15	15	0.3	0.3
Paratyphoid fever	16	59	0.4	1.3
Epidemic cerebrospinal meningitis	114	131	2.5	2.9
Acute anterior poliomyelitis, total	16	154	0.4	3.4
—, paralytic	10	37	0.2	0.8
Epidemic cerebrospinal meningitis	34	17	0.8	0.4
Dysentery	114	63	2.5	1.4
Intermittent fever, originating in Denmark	—	—	—	—
—, outside Denmark	12	8	0.3	0.2
Diphtheria	—	—	—	—
Scarlet fever	2,295	2,639	51.1	59.1
Puerperal fever	21	30	2.8[2])	3.9[2])
Pemphigus neonatorum[1])	196	215	25.6[3])	28.0[3])
Tetanus neonatorum[1])	8	19	1.0[3])	2.5[3])
Measles	57,371	45,420	1,278.4	1,016.9
German measles	10,668	9,000	237.7	201.5
Chicken-pox	21,600	24,986	481.3	559.4
Whooping-cough	66,588	68,560	1,483.8	1,535.0
Mumps	24,456	30,964	544.9	693.3
Influenza	544,613	115,203	12,135.4	2,579.3
Angina and tonsillitis	178,444	182,700	3,976.2	4,090.5
Tracheobronchitis	109,839	117,635	2,447.5	2,633.8
Bronchopneumonia	47,086	42,197	1,049.2	944.8
Lobar pneumonia	4,744	4,947	105.7	110.8
Cholerine and enteritis	49,961	62,167	1,113.3	1,391.9
Epidemic hepatitis	3,356	5,385	74.8	120.6
Rheumatic fever	983	1,142	21.9	25.6
Erysipelas	2,851	3,078	62.9	69.9
Gonorrhoea, not previously diagnosed	7,447	7,665	165.9	171.6
Soft chancre, not previously diagnosed	9	14	0.2	0.3
Acquired syphilis, not previously diagnosed	48	104	1.1	2.3
Congenital syphilis, not previously diagnosed	6	4	0.1	0.1
Lymphogranuloma inguinale	7	4	0.2	0.1
Delirium tremens	56	58	1.2	1.3
Scabies	2,453	3,877	54.7	86.8

[1]) Under one month. [2]) per 10,000 parturients. [3]) per 10,000 live-born.

Table 3.

Notifiable diseases according to age 1957 and 1956.

Age	Reported cases 1957	per 1,000 population 1957	1956
0— 1 year	46,664	618	576
1— 4 years	219,835	738	607
5—14 »	312,113	384	249
15—64 » males	243,323	173	90
15—64 » females	239,583	166	86
65 years and over, m.	31,490	148	101
65 years and over, f.	32,377	134	86
Total	1,125,385	251	160

Table 4.

Deaths per 1,000 population by age and sex. 1957 and 1921.

	1957		1921	
	M	F	M	F
Under 1 year	27.3	19.0	87.9	67.2
1— 4 years	1.2	1.1	5.6	4.4
5—14 »	0.4	0.3	1.7	1.7
15—25 »	0.9	0.5	2.9	2.7
25—34 »	1.2	1.0	3.5	3.7
35—44 »	2.3	1.9	4.4	5.4
45—54 »	5.8	4.2	8.7	8.6
55—64 »	16.0	10.5	18.2	17.1
65 years and over	66.2	58.1	70.4	70.8
Total	9.9	8.7	11.2	11.2

in 1956. No cases of diphtheria were reported in 1956 and 1957.

Since 1954 a slightly decreasing tendency has been observed in the number of reported cases of gonorrhoea, 7,447 cases being notified in 1957; of these about one half occurred in Copenhagen. In 1957 48 cases of acquired syphilis were notified, hereof 22 in Copenhagen. The total number of cases of this disease was in 1956 104.

The distribution of notifiable diseases by age, shown in Table 3, indicates that the epidemic morbidity has been increasing from 1956 to 1957 in all age-groups, but only slightly for children below 1 year.

As shown in Table 1 the crude mortality rate increased in 1957 to 9.3 per 1,000 as against 8.9 in 1956. It will be seen from Table 4 that the decrease in mortality rate since 1921 has been heavier for females than for males, and more pronounced in the younger age groups.

The infant mortality rate is continously decreasing, and the drop was larger from 1956 to

Table 5.

Causes of Death in Denmark 1957 and 1956. Abbreviated List (B).

			1957			1956	Per 100,000 pop. 1957			1956
			M	F	Total	Total	M	F	Total	Total
B	1	Tuberculosis of respiratory system	115	55	170	191	5.2	2.4	3.8	4.3
B	2	Tuberculosis, other forms	16	13	29	36	0.7	0.6	0.6	0.8
B	3	Syphilis and its sequelae	50	27	77	79	2.2	1.2	1.7	1.8
B	4	Typhoid fever	1	—	1	—	0.0	—	0.0	—
B	6	Dysentery, all forms	—	1	1	2	—	0.0	0.0	0.0
B	7	Scarlet fever and streptococcal sore throat	2	—	2	7	0.1	—	0.0	0.2
B	8	Diphtheria	—	—	—	—	—	—	—	—
B	9	Whooping cough	12	13	25	17	0.5	0.6	0.6	0.4
B	10	Meningococcal infections	3	4	7	3	0.1	0.2	0.2	0.1
B	12	Acute poliomyelitis	—	—	—	—	—	—	—	—
B	14	Measles	7	5	12	8	0.3	0.2	0.3	0.2
B	17	All other diseases classified as infections and parasitic	60	65	125	142	2.7	2.9	2.8	3.2
B	18	Malign. neoplasms, incl. neoplasms of lymph. and haematopoietic tissues	4,440	4,569	9,009	8,764	199.6	201.9	200.7	196.2
B	19	Benign and unspecified neoplasms	165	174	339	351	7.4	7.7	7.6	7.9
B	20	Diabetes mellitus	124	185	309	312	5.6	8.2	6.9	7.0
B	21	Anæmias	40	55	95	95	1.8	2.4	2.1	2.1
B	22	Vasc. lesions affect. central nervous system	2,490	2,816	5,306	5,115	111.9	124.4	118.2	114.5
B	23	Nonmeningococcal meningitis	34	17	51	40	1.5	0.7	1.1	0.9
B	24	Rheumatic fever	5	9	14	16	0.2	0.4	0.3	0.4
B	25	Chronic rheumatic heart disease	113	227	340	280	5.1	10.0	7.6	6.3
B	26	Arteriosclerotic and degenerative heart disease	5,924	4,264	10,188	9,506	266.3	188.4	227.0	212.8
B	27	Other diseases of heart	1,079	1,006	2,085	1,879	48.5	44.4	46.5	42.1
B	28	Hypertension with heart disease	282	459	741	817	12.7	20.3	16.5	18.3
B	29	Hypertension without mention of heart	55	82	137	184	2.5	3.6	3.1	4.1
B	30	Influenza	227	208	435	42	10.2	9.2	9.7	0.9
B	31	Pneumonia	416	439	855	785	18.7	19.4	19.1	17.6
B	32	Bronchitis	166	114	280	203	7.5	5.0	6.2	4.5
B	33	Ulcer of stomach and duodenum	210	68	278	267	9.4	3.0	6.2	6.0
B	34	Appendicitis	54	34	88	95	2.4	1.5	2.0	2.1
B	35	Intestinal obstruction and hernia	143	145	288	296	6.4	6.4	6.4	6.6
B	36	Gastritis, duodenitis, enteritis and colitis, except diarrhoea of the newborn	59	95	154	166	2.7	4.2	3.4	3.7
B	37	Cirrhosis of liver	171	209	380	286	7.7	9.2	8.5	6.4
B	38	Nephritis and nephrosis	119	105	224	251	5.4	4.6	5.0	5.6
B	39	Hyperplasia og prostate	540	—	540	571	24.3	—	12.0	12.8
B	40	Complications of pregnancy, childbirth and the puerperium	—	31	31	37	—	1.4	0.7	0.8
B	41	Congenital malformations	232	180	412	443	10.4	8.0	9.2	9.9
B	42	Birth injuries, postnatal asphyxia and atelectasis	313	205	518	541	14.1	9.1	11.5	12.1
B	43	Infections of the newborn	21	15	36	14	0.9	0.7	0.8	0.3
B	44	Other diseases peculiar to early infancy, and immaturity unqualified	290	196	486	585	13.0	8.7	10.8	13.1
B	45	Senility without mention of psychosis, ill-defined and unknown causes	248	279	527	482	11.2	12.3	11.7	10.8
B	46	All other diseases	1,878	2,247	4,125	3,690	84.4	99.3	91.9	82.6
BN	47	Fractures, head injuries and internal injuries	893	699	1,592	1,606	40.1	30.9	35.5	35.9
BN	48	Burns	28	22	50	45	1.3	1.0	1.1	1.0
BN	49	Effects of poisons	406	296	702	650	18.3	13.1	15.7	14.6
BN	50	All other injuries	511	155	666	689	23.0	6.8	14.8	15.4
Total			21,942	19,788	41,730	39,590	986.3	874.3	929.9	886.4
		Alternative classification of deaths from accidents, poisoning, and violence (BN 47 — BN 50) according to external cause:								
BE	47	Motor vehicle accidents	488	161	649	646	22.0	7.1	14.5	14.5
BE	48	All other accidents	679	667	1,346	1,297	30.5	29.5	30.0	29.0
BE	49	Suicide and self-inflicted injury	660	331	991	1,004	29.7	14.6	22.1	22.5
BE	50	Homicide and operations of war	11	13	24	44	0.5	0.6	0.5	1.0

1957 than during the previous year, the rate being 25.2, 24.9 and 23.4 per 1,000 live-born respectively in 1955, 1956 and 1957.

From Table 5 will be seen that malignant neoplasms and arteriosclerotic and degenerative heart diseases are the two leading causes of death in 1957, as in previous years. These two groups now make up 46 per cent of all deaths.

The greatest increase in the number of deaths occurred in the two groups just mentioned, and

Table 6.

Notification rate, mortality rate, and lethality for influenza in 1956 and 1957.

	1956			1957		
	Per 100,000 pop.		Lethality, deaths per 1,000 not. cases	Per 100,000 pop.		Lethality, deaths per 1,000 not. cases
	Notified cases	Deaths		Notified cases	Deaths	
Under 1 year	2,071	2.67	1.29	9,127	9.27	1.02
1— 4 years	3,218	0.34	0.10	19,579	4.03	0.22
5—14 »	2,510	—	—	16,535	1.72	0.10
15—64 » males	2,828	0.21	0.08	11,502	4.34	0.38
15—64 » females	2,627	0.14	0.05	10,964	3.12	0.28
65 years and over, males	1,562	9.14	5.85	6,519	69.44	10.65
65 years and over, females	1,299	6.36	4.90	5,947	61.65	10.37
Total	2,580	0.94	0.36	12,135	9.69	0.80

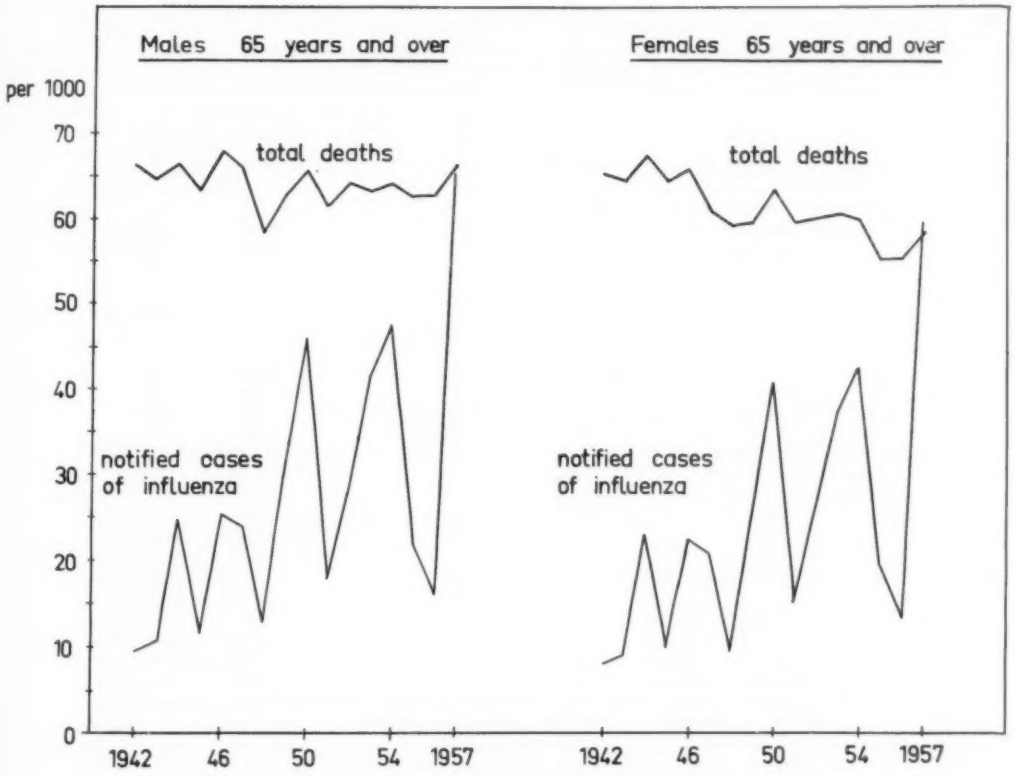

Figure 1.

Total deaths and notified cases of influenza per 1,000 population. Males and Females aged 65 years and over. Denmark 1942—57.

Table 7.

Pulmonary tuberculosis by age and sex 1956.

	Notified cases		Known cases Dec. 31st 1956	
	M	F	M	F
0— 4 years	46	52	110	111
5—14 »	40	41	372	319
15—24 »	41	66	428	687
25—44 »	185	202	2,785	3,384
45—64 »	225	86	2,053	1,309
65 years and over	72	71	603	416
Total	609	518	6,351	6,226

for influenza and the group "All other diseases". The number of deaths from influenza was in 1957 ten times that of 1956.

Table 6 shows the number of reported cases of and deaths from influenza per 100,000 population, and the lethality rate in 1956 and 1957. Both the rate of reported cases and of deaths have been increasing for all age groups, but not to the same degree. Notified cases has risen to about five times the 1956-level, but there are great differences between the age groups. Infants and adults show an increase of about four times, whereas

Table 8.
Number of visits to physicians and midwives according to Act concerning Pregnancy Hygiene.

	1956/57	1951/56 average	1946/51	1946/47
1st visit to physician	74,416	71,482	69,622	71,990
Utilization (*i.e.* 1st visit in per cent of live-born children)	107[1]) 90[2])	103[1]) 85[2])	90[1]) 72[2])	83[1]) 65[2])
2nd and 3rd visit to physician	110,229	102,309	95,033	90,019
Utilization (*i.e.* 2nd and 3rd visit in per cent of 1st visit)	74[1]) 74[2])	72[1]) 71[2])	72[1]) 64[2])	71[1]) 54[2])
Visits to midwives (maximum 7)	301,958	287,321	266,581	260,533
Utilization (*i.e.* visits to midwives in per cent of 1st visit to physicians)	64[1]) 53[2])	64[1]) 52[2])	63[1]) 47[2])	62[1]) 41[2])
Number of live-born children in calendar year	76,700	77,000	87,140	96,100

[1]) Towns. [2]) Rural districts.

Table 9.
Beds in hospitals and other institutions for treatment of the sick. December 31st 1956.

	No. of institutions	No. of departments	No. of beds total	No. of beds per 1,000 population
1. Hospitals:				
Hospitals with special departments	72	247	20,150	4.51
Hospitals mostly with mixed departments	73	76	5,788	1.30
viz. { mixed departments		70	5,305	1.19
viz. { special departments		6	483	0.11
All hospitals	145	323	25,938	5.81
2. Other institutions:				
Infirmaries in old-age homes etc.	58	—	3,280	0.73
Private clinics	16	—	338	0.08
Municipal maternity hospitals	3	—	104	0.02
Nursing institutions	45	—	2,834	0.63
Tuberculosis hospitals	33	—	2,472	0.55
Mental hospitals	10	—	9,334[1])	2.09
Hospitals for epileptics	3	—	1,049	0.23
Total	168	—	19,411	4.34
All hospitals and institutions	313	—	45,349	10.15
In addition accomodation in:				
Asylums for feeble-minded			7,364[2])	1.65
Institutions for the blind			379	0.08
Institutions for deaf-mutes			626	0.14

See table 11 concerning activity of special departments.
[1]) In addition accommodation for 980 patients in family nursing.
[2]) In addition accommodation for 7,299 patients in family nursing.

children aged 1—14 years have about six times as many reported cases in 1957 as in 1956. The mortality rate from influenza has been increasing ten times. The heaviest increase, namely 20 times, occured in the age group 15—64 years. The lethality, expressed as number of deaths per 1,000 notified cases, has been doubled. The age groups differ also in this respect, the lethality for the 15—64 year age group having increased five times, whereas the infants seem to have a slightly decreasing lethality.

An investigation of the correlation between the rate of notified cases of influenza, and the total mortality during the years 1942—57 has been carried out. It was not possible to show any connection for the ages below 65 years, whereas there seems to be a pronounced tendency to high mortality rate in years with high notification rate of influenza for the age group 65 years and over, as can be seen from Figure 1.

Table 5 also shows that the mortality from tuberculosis continues to decrease, the mortality from pulmonary tuberculosis being 3.8 per 100,000 in 1957, and the mortality from all forms of tuberculosis 4.4. Thus deaths from tuberculosis amount to less than one third of deaths from motor vehicle accidents.

Table 10.

Survey of Cases admitted to Danish General Hospitals. 1956, 1950 and 1945.

	Main diagnoses			per 1,000 diagnoses			
	1956	1955	1950	1956	1955	1950	
1 Respiratory diseases	21,795	19,810	23,441	42.5	39.6	52.0	1
2 Senile diseases	611	733	776	1.2	1.5	1.7	2
3 Diseases of musculo-skeletal system	23,287	23,726	20,195	45.4	47.4	44.8	3
4 Diseases of the blood and blood-forming organs	3,855	3,649	3,036	7.5	7.3	6.7	4
5 Endocrine diseases	16,289	15,623	12,158	31.8	31.2	27.0	5
6 Diseases of the digestive system	77,694	80,316	70,702	151.6	160.4	156.8	6
7a Poisonings, acute	5,153	5,291	3,276	10.0	10.6	7.3	7a
7b Poisonings, chronic	1,350	1,366	1,009	2.6	2.7	2.2	7b
8 Skin diseases	13,492	13,180	16,004	26.3	26.3	35.5	8
9 Infectious diseases*)	17,617	18,192	26,501	34.4	36.3	58.8	9
10 Diseases of the circulatory system	34,343	33,362	24,752	67.0	66.6	54.9	10
11a Diseases of the genitals, male (excl. venerea)	7,204	6,829	5,705	14.1	13.6	12.7	11a
11b Diseases of the genitals, female (excl. venerea)	36,661	35,076	28,694	71.5	70.0	63.6	11b
12 Malformations, congenital	3,700	3,318	2,480	7.2	6.6	5.5	12
13 Organic diseases of the nervous system	16,858	15,896	12,778	32.9	31.7	28.3	13
14 Functional diseases of the nervous system	22,758	22,461	22,285	44.4	44.8	49.4	14
15 Infantile diseases	3,158	2,979	2,272	6.2	5.9	5.0	15
16 Diseases of the urinary system	13,884	13,204	10,308	27.1	26.4	22.9	16
17 Diseases of pregnancy and childbirth	31,516	29,733	26,000	61.5	59.4	57.7	17
18 Normal pregnancy and birth	44,924	44,867	43,024	87.6	89.6	95.4	18
19a Tumours, malignant	19,937	19,252	15,237	38.9	38.4	33.8	19a
19b Tumours, benignant	13,652	12,715	10,195	26.6	25.4	22.6	19b
20 Traumatic injuries	53,142	49,973	37,823	103.7	99.8	83.9	20
21 Eye diseases	7,040	6,210	6,201	13.7	12.4	13.8	21
22 Ear diseases	7,181	7,566	10,661	14.0	15.1	23.6	22
23 Observations and other uncertain cases	15,525	15,517	15,368	30.3	31.0	34.1	23
Total	512,626	500,844	450,881	1,000.0	1,000.0	1,000.0	
per 1,000 population	115	113	106	—	—	—	
*) hereof venereal diseases	793	861	1,415	1.5	1.7	3.1	

Table 11.

Number of beds, admissions and average length of stay in special departments in Danish hospitals 1955/56.

Departments	No. of departments	No. of beds	Admissions	Average length of stay in days	
				1956	1955
Medical	57	6,316	98,870	21	22
Surgical	54	6,219	151,710	15	15
Neurological	6	456	8,492	21	22
Brain-surgical	4	188	4,449	17	14
Chest-surgical	2	119	1,460	25	23
Orthopaedic	6	447	8,052	21	22
Gynaecological	15	1,086	31,433	12	12
Maternal	6	394	11,631	11	11
Otolaryngological	25	707	19,159	11	11
Ophthalmological	20	317	5,795	15	16
Paediatric	13	900	11,780	25	25
Dermato-venereal	7	496	5,686	28	26
Radium	3	302	4,289	25	24
X-ray	1	27	220	37	34
Fysiurgic	3	73	825	32	32
Epidemic	5	630	8,747	19	20
Psychiatric	6	612	11,382	22	21
Tuberculosis	17	922	3,986	62	68
Total 1956	250	20,211	387,966	—	—
Total 1955	246	19,936	376,488	—	—

The number of notified cases of pulmonary tuberculosis decreased in 1956 by 109 to 1,127 cases, or 25 per 100,000 population, as against 28 in 1955. The number of known cases of pulmonary tuberculosis at the end of 1956 was 12,577 or 282 per 100,000. The age distribution of notified cases in 1956 and known cases as of December 31st 1956 is shown in Table 7.

80.6 per cent of all notified cases of pulmonary tuberculosis were bacillary, against 81.0 per cent in 1955.

161 cases of extrapulmonary tuberculosis or 3.6 per 100,000 population were notified in 1956 against 194 or 4.4 per 100,000 in 1955. There were

103 chest clinics in Denmark in 1956. 930,166 persons were examined, and 1,386,756 consultations and 46,338 BCG-vaccinations were given.

According to law, pregnant women can have 10 examinations free of charge, 3 by physician and 7 by midwife. In 1956/57 the number of visits to physicians and midwives were 184,645 and 301,958 respectively. Table 8 shows the utilization rate during later years in rural and urban areas. The rate seems much higher in towns than in rural areas, and sometimes exceeds 100 per cent. The reason for this is that a number of women, living in rural areas visit physicians in the towns, and therefore are registered under urban areas.

The number of Public Health Nurses for infants was 358 at the end of 1957 against 356 in 1956. 47,742 infants, or 62.2 per cent of all live-born, were supervised at the end of the year, as against 61.1 per cent in 1955. Only 509, or 1.0 per cent of the homes refused to receive the Public Health Nurse. 824,731 visits were paid.

189 of the aforementioned Public Health Nurses were also working as School Nurses, and 60 nurses worked exclusively as such. The corresponding figures for 1955 were 56 and 63 respectively.

At the end of the school-year 1956/57 dental services were given to school children in the Capital, and in some towns and rural areas. 305 dentists were working in this field, hereof 120 in the Capital, 115 in other towns and 70 in rural areas. The capital, 46 urban and 42 rural municipalities had established dental clinics for the school children, and in a few municipalities dental services were rendered by practising dentists in their office.

School meals were in 1956/57 given in 72 municipalities, and 216,100 children attended. 10 million meals and 29.6 million bottles of milk were served. Expenditure amounted to 12.9 million Danish crowns. The rate of children attending school meals in the Capital was 97 per cent and in the rest of the country 68 per cent of those offered this service.

A survey of the number of beds in hospitals and other institutions for care of the sick is given in Table 9. There were 25,938 beds in 145 hospitals, and 19,411 in other institutions. The total number of beds amounts to 10.15 per 1,000 population.

Table 10 gives information about cases treated in the hospitals in 1950, 1955 and 1956.

The number has been increasing, and was 115 per 1,000 population in 1956 as against 113 and 106 in 1955 and 1950 respectively. The number of cases, 512,626, exceeds the number of patients, because in some cases more than one diagnosis is given. A change in the relative frequency of the diagnosis-groups has taken place during later years. Some groups are now more frequent than before, e.g. diseases of the circulatory system, diseases of pregnancy and childbirth, neoplasms and traumatic injuries. There are on the other hand relatively fewer cases of skin diseases and infectious diseases, including V.D. The total number in these two groups has decreased from 75,400 in 1945 (17.5 per cent) to 31,100 in 1956 (6.1 per cent), a decrease which alone has enabled the hospitals to treat about 44,000 additional patients with other diseases.

A total of 498,244 patients were treated in the hospitals in 1956. The number of bed-days was 8.8 million, and the average length of stay 18 days.

The activity of the special hospital departments is shown in Table 11. These departments with a total of 20,211 beds, treated 387,966 patients. The number of bed-days per patient was roughly the same in 1955 and 1956, viz, for surgical departments 15 in both years, and for medical departments 21 and 22 days respectively.

The working expenses of the public hospitals in 1955/56 were 353.4 million Danish crowns, against 323.5 million in 1954/55 (see Table 12). The largest entry was wages with almost 60 per cent of the total. The relatively greatest increase in expenses from 1954/55 to 1955/56 occurred for the entry "Other expenses", causing a slight decrease in the percentage of expenses for wages and board.

Table 12.

Working expenses of all public hospitals 1955/56. In Danish crowns (1 D.cr. — 1 sh. — 0,14 U.S.$).

	Total in mill. D.cr.	In per cent of total: Wages	Board	Other expenses
County and municipal hospitals	315.3	59.2	9.7	31.1
State hospitals	38.1	64.9	6.7	28.4
Total 1955/56	353.4	59.8	9.4	30.8
Total 1954/55	323.5	59.9	9.5	30.6

The average expense per bed-day in 1955/56 was 44.92 Danish crowns, against 41.03 Danish crowns in 1954/55, and the expense per board-day was 2.75 Danish crowns against 2.53 in the previous year. The total expense per capita was 79.12 Danish crowns in 1955/56 and 72.86 in 1954/55.

The total number of physicians employed in the public hospitals in 1956 was 1,739, hereof 1,518 in city- and county hospitals. 7,111 registered nurses were working in the public hospitals, of whom 6,136 were in city- and county hospitals. The number of student nurses was 4,133 in public hospitals, hereof 3,932 in city- and county hospitals. In all hospitals, public as well as private, there were 2,002 physicians, 8,055 registered nurses and 4,398 student nurses. A total of 2,288 physicians were employed by all curative institutions; of these 574 were chief physicians.